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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1956

ORIGINAL ARTICLES

SALICYLATE INGESTION: A FREQUENT CAUSE OF GASTRIC HEMORRHAGE

By J. J. Kelly, Jr., M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Department of Medicine, State University of New York College of Medicine at New York City and the Kings County Hospital, Brooklyn, New York)

Although the salicylates, as decoctions of willow bark, were used in folk medicine since the time of Hippocrates, it was not until 1876 that they were introduced into scientific medicine. By 1877 it had been learned that these substances were capable of producing nausea, vomiting, epigastric distress and occasionally gastrointestinal hemorrhage. At first these toxic effects were thought to be due to local irritating effects on the gastrointestinal tract, but later they were seen to follow parenteral administration of these drugs[15].*

The classic researches of Link[28] led to a fuller understanding of the mechanism of hemorrhage in salicylate poisoning when he and his associates demonstrated that salicylate compounds could induce a hypoprothrombinemia in certain laboratory animals. The hypoprothrombinemic effect of salicylates was soon demonstrated in man[30,35]. In the following years, there were reports of many cases of purpura and hemorrhages into various sites of the body due to hypoprothrombinemia induced by salicylate poisoning[15]. Bleeding due to the hypoprothrombinemic effect of salicylates is now widely recognized.

However, gastrointestinal bleeding may occur following small doses of aspirin, with little or no demonstrable change in the prothrombin concentration of the blood. Hurst and Lintott[21], in 1939, described a patient who experienced severe migraine and repeated episodes of unexplained gastrointestinal bleeding over many years. The relationship between the ingestion of aspirin and bleeding was established. These authors gastroscoped this subject and noted hyperemia and bleeding of the gastric mucosa where it came into contact with two aspirin tablets given after the gastroscope was in place. Crismer[8], in 1947, reported 2 patients in whom gastrointestinal hemorrhage seemed related to the ingestion of small amounts of salicylate.

Warthin[41] states in a brief note in his monograph on gastrointestinal bleeding that salicylates may cause

*For the sake of brevity many references have been omitted which can be easily found in the monograph of Gross and Greenberg[15].

hemorrhage, particularly in elderly subjects with arthritis who develop gastric allergy to this drug.

More recently Muir and Cassar[31] drew attention to the frequency in which hemorrhage occurred in ulcer patients following aspirin.

We wish to report the following cases of gastrointestinal bleeding in which we believe acetyl salicylate to be related to the melena although the well known hypoprothrombinemic effects of the salicylates were not evident.

Case Reports. CASE 1. C.K. This 62-year-old housewife, with 8 children, was in apparent good health until 1946 when her family, alarmed by her evident weakness and pallor, forced her to consult a physician. The only symptoms admitted by the patient were increasing weakness during the preceding year, frequent attacks of laryngitis and bronchitis for the past few winters and episodes of headaches dating back about 10 years. The past history was unremarkable except for a thyroidectomy in 1931, for relief of a colloid goitre. There was no family history suggestive of peptic ulcer or hemorrhagic tendencies. She was a pale, somewhat obese white woman with a moderate diastolic hypertension. The hemoglobin was 7 gm. % and the stool was tarry. Laboratory investigation included a gastrointestinal series and a barium enema which were considered normal. Free hydrochloric acid was found on gastric aspiration.

It was presumed that this woman suffered from a "silent" peptic ulcer. Therefore, she was advised to avoid spicy foods and to take frequent feedings. Ferrous sulfate was prescribed for the anemia and in 2 months the hemoglobin rose to 14 gm.

From 1946 to 1954, she experienced numerous episodes of weakness which were secondary to blood loss. Yet never did she notice any digestive disturbance or abdominal pain. The anemia would respond nicely to iron and when the patient continued ferrous sulfate therapy she would feel quite well. With the return of her strength, she would discontinue the administration of iron and soon afterwards would again experience weakness and tarry stools.

In 1948 and 1950, this woman was subjected to intensive investigations at another University Medical Center where no gastrointestinal lesion was found except a diverticulum of the large bowel. Free hydrochloric acid was present in the fasting gastric juice on both of these hospital admissions. No evidence of liver disease or of a hematological defect was found.

In February, 1954, questioning of the patient brought out the fact that the melena followed episodes of headache which in turn were treated with aspirin. The amount of aspirin ingested never exceeded 8 tablets a day (2.4 gm.).

Because of the possibility that the melena may have resulted from either salicylate intoxication or sensitivity, it was decided to observe the results of salicylate by having the patient ingest 0.6 gm. acetyl salicylate acid four times a day. After 2 days of aspirin ingestion, the stools turned from guaiac-negative to positive and by the third day the stool was tarry. Her hemoglobin dropped from 12 to 10.5 gm. The aspirin was stopped and in 2 days the melena disappeared; 2 days later the stools were completely free of occult blood. Again aspirin in the same dosage was administered. Within 48 hours the stools were guaiac-positive, although no further drop in the hemoglobin occurred. Daily determinations of the prothrombin time during this period of observation were within normal limits and showed no change.

It was concluded from these observations that the aspirin played a causative role in the gastrointestinal bleeding of this patient, without causing hypoprothrombinemia. The small doses which evoked bleeding were noted, and she was cautioned against the use of salicylates in any form. In the 19-month follow-up there have been no instances of melena and for the first time in 9 years it has been possible to maintain a normal hemoglobin level without recourse to ferrous sulfate.

CASE 2. M.R. This man, at the age of 29, first sought medical attention because of severe headaches and weakness. The diagnosis of acromegaly was made and the headaches where attributed to this condition. The weakness, however was secondary to a severe anemia which was thought to be due to upper gastrointestinal hemorrhage, as the patient admitted to passage of tarry stools. The patient denied any symptoms referable to the gastrointestinal tract except for heartburn which he experienced occasionally after the ingestion of aspirin.

Between 1931 and 1946 the patient was admitted to the Kings County Hospital on ten occasions with essentially the same clinical picture and findings. All admissions were

prompted by weakness secondary to anemia. The stools were always tarry on admission but repeated gastrointestinal series failed to disclose a lesion. Free acid was found in the fasting gastric specimen on several occasions. There was no evidence of liver disease. Hematological investigation revealed normal clot retraction, normal capillary fragility, bleeding and clotting time, but prothrombin time was not measured.

On the eleventh hospital admission, in October, 1946, he had the usual symptoms of weakness, anemia and tarry stools. At this time, the physical examination demonstrated a pale man with the typical skeletal features of acromegaly. His stool was tarry and positive for blood. During 4 days in the hospital his hemoglobin dropped from 10 to 7 gm. in spite of 1500 ml. of blood received by transfusion. The stools remained grossly tarry. At this time it was noted that the melena always followed episodes of headache treated with aspirin, and on that admission, the patient had been receiving 0.6 gm. acetyl salicylic acid every four hours. The aspirin was stopped and codeine was substituted for relief of the headache. Within 72 hours after the discontinuation of aspirin, the stools were only faintly positive for occult blood and a day later the guaiac test was negative.

It was felt that the repeated bouts of melena represented a hypersensitivity of the gastric mucosa to salicylates and that this case was quite similar to that of Hurst and Lintott[21]. Therefore, the patient was advised strongly against the use of salicylates in any form. Aminopyrine or codeine was prescribed for the relief of his headaches.

Early in 1947, his supply of aminopyrine exhausted, he purchased a proprietory headache compound which contained acetyl salicylic acid. After ingesting these tablets over a period of several days, he again became weak and noted tarry stools. He entered another hospital where gastric exploration was carried out after several transfusions. At operation a hemorrhagic gastritis was found. A subtotal gastric resection was carried out from which the patient made an uneventful recovery.

In the following 7 years there have been no instances of melena nor any further hospital admissions. His headaches occur more rarely and are less intense when they do occur. He rarely uses aspirin now, yet on the few occasions which he did take a salicylate compound, no melena was noted.

CASE 3. J.B. This 53-year-old Negro laboratory technician had fifteen hospital admissions between the years 1936 and 1949 for painless gastrointestinal hemorrhage. The patient denied at all times any symptoms suggestive of a peptic ulcer. He repeatedly brought to the attention of the interviewing physicians that the melena occurred during prolonged migraine attacks.

During his many hospital admissions, the physical examination revealed nothing remarkable aside from pallor and tarry stools. At times the bleeding was severe enough to produce an anemia requiring immediate blood transfusion. Repeated radiological examinations of the gastrointestinal tract were done without uncovering a lesion. Free acid was found in the fasting specimens of gastric juice on three occasions. The prothrombin time, bleeding, and clotting times and capillary fragility, all were within normal limits. These tests were done when the patient was exhibiting evidence of continued gastrointestinal bleeding.

Perusal of the nurses' chart notes brought to light a clear relationship between the ingestion of salicylates and the melena. On two occasions the patient continued to bleed while in the hospital. During these periods the nurses' notes record the fact that the patient continually complained of severe headache for which he received 0.6 acetyl salicylic acid every 4 hours (3.6 gm. in 24 hours). With relief of the migraine attack and the cessation of salicylate therapy, the stools rapidly became free of blood. The prothrombin time determined during one of these episodes was within normal limits.

Unfortunately, the house staff were not impressed by the nurses' notes or the repeated statements of the patient on the close association of the melena with migraine attacks. In October, 1949, the patient was subjected to a gastric exploration. At operation a small, shallow prepyloric ulcer and gastritis were found. An extensive subtotal gastrectomy was done from which the patient made an uneventful recovery.

Since this time the patient has noted no further melena and he has continued to feel well. The migraine rarely occurs which the patient attributes to the solution of marital difficulties by a divorce which was granted just before the operation in 1949. With the absence of migraine, he very rarely uses aspirin.

"UNEXPLAINED GASTRIC HEMORRHAGE" ASSOCIATED WITH SALICYLATE INGESTION. This experience prompted an examination of the hospital records of patients with unexplained upper gastrointestinal

bleeding for similar cases. In a 4-year period, there occurred 49 cases which were investigated thoroughly enough to exclude the common causes of gastrointestinal hemorrhage (peptic ulcer, gastric cancer, esophogeal varices, and hiatus hernia). It was striking that in these 49 records there were 16 instances where a history of salicylate therapy was in progress for other conditions when the bleeding occurred. These illnesses are listed in Table 1.

aspirin or any medication which can be purchased without a prescription a drug. This point is strongly emphasized by Muir and Cassar[31] who questioned a large series of patients in detail concerning the use of salicylates.

Nevertheless there is a striking difference between the 32% incidence of salicylate ingestion in the group with the unexplained gastrointestinal bleeding and the 4% incidence in the control group. This is strong circumstan-

TABLE 1.—

	Illnesses Treated with Salicylates Prior to Bleeding	*Number of Patients*
Group with unexplained upper gastrointestinal hemorrhage	Severe headaches	8
	Arthritis	6
	Grippe	1
	Chest injury	1
	Total	16 = 32% of Group
Group with bleeding from proven peptic ulcer	Headache	9
	Arthritis	5
	Grippe	1
	Total	15 = 30% of Group
Control Group: patients with acute myocardial infarction and no gastrointestinal bleeding	Headache	2
	Arthritis	1
	Bursitis	1
	Total	4 = 4% of Group

Three of this group had two or more episodes of hemorrhage which were associated with salicylate ingestion. As a control, the histories of 100 patients with myocardial infarction were reviewed for the frequency which aspirin-ingestion preceded the symptoms of myocardial infarction. Only 4 instances were found where prior ingestion of aspirin, headache or arthritis were associated with this disorder.

These data were obtained by review of the hospital records, therefore the frequency of salicylate use would undoubtedly be higher if each patient were questioned specifically about aspirin or other drugs containing salicylate. All of these subjects were queried concerning the use of drugs, but unfortunately most patients do not consider

tial evidence that there is a causal relationship between salicylates and the gastrointestinal bleeding of these patients.

Discussion. As an index of the frequency of this phenomenon, the experience of Sir Arthur Hurst[20] is worth noting. Between the years 1939 and 1943, he had seen 58 patients with upper gastrointestinal hemorrhage in whom peptic ulcer, carcinoma of the stomach, or esophogeal varices could be excluded. Hurst credited aspirin as the cause of the hemorrhage in one-half of this group.

The histories of the patients in this group are quite similar. The following 2 abbreviated case histories are given as illustrations of this. A middle-aged male with no previous dyspepsia de-

veloped a persistent and severe headache which could be partially relieved by aspirin. After a week of the headache, gastrointestinal bleeding would be discovered. The other typical history is that of an elderly woman who enjoyed good health until 2 weeks prior to the hospital admission when she developed acute osteoarthritis which was treated with salicylates. After a week or so of aspirin, she would experience progressive weakness, melena or hematemesis, or both, which would prompt hospital admission.

The patients of this series were similar in the following respects: a) melena in the absence of the usual ulcer symptoms, b) bleeding occurred after the ingestion of salicylates but not through the hypoprothrombinemic effects of these compounds, 3) no roentgenographic proof of an ulcer, d) free acid present in the fasting stomach contents.

In a comprehensive study of the relation of aspirin to ulcer, Muir and Cassar[31] have included 21 patients similar to ours in a series of 166 cases of hematemesis. The remainder of this group had either proven gastric or duodenal ulcer. These authors labeled those patients with hematemesis but no previous digestive symptoms and no subsequent laboratory evidence of an ulcer as the "acute lesion group." It is impossible from their data to estimate what fraction this group constitutes of all patients with upper gastrointestinal hemorrhage not associated with proven ulcer, cancer of the stomach, varices or hiatus hernia. It must be quite high, as the total number of cases of ulcer hematemesis which includes this group is only 166.

Of these 166 instances of hematemesis, 73 patients admitted to ingestion of salicylate within 24 hours of the hematemesis and 54 to within 6 hours. Considering these 54 patients in more detail, 11 were found to take aspirin so frequently that there was no probable relationship between the salicylate and the hemorrhage. However, in the remaining 43, the evidence strongly indicated that the aspirin was the major factor precipitating the hematemesis.

Elsewhere in the same report, Muir and Cassar demonstrated that salicylate was a common cause of recrudescence of a peptic ulcer symptom as well as a cause of hematemesis.

Because of this and for other reasons which will be discussed later, the records of patients with bleeding proven peptic ulcer were examined in a manner similar to that done earlier. In a 12-month period, 75 patients with a bleeding peptic ulcer were admitted to the University Division of the Kings County Hospital. Of this total, 15 (20%) were receiving salicylates when symptoms developed. This high incidence of aspirin users among patients with bleeding peptic ulcer is not proof that salicylates were responsible for bleeding but does support the contention of Muir and Cassar that aspirin is a frequent cause of peptic ulcer activity.

Cases 1 to 3 bear a strong resemblance to that of Hurst and Lintott[21] in that the multiple episodes of melena were always preceded by headache which was treated by aspirin. The close association of the bleeding with the ingestion of salicylate and the absence of the usual ulcer symptoms suggests that the gastroduodenal mucosa of these patients responded to aspirin in an allergic manner. By gastroscopy Hurst and Lintott were able to view the reaction of the gastric mucosa of their subject which came into contact with aspirin given after the gastroscope was in place. They observed hyperemia and ulceration of the mucosa in contact with the particles of aspirin. Implicit in their report is that this response of the mucosa of their patient

was a matter of drug idiosyncrasy. Later Lintott and Douthwaite[10] reported that mucosal hyperemia was a common reaction of the asymptomatic subject to ingested aspirin in a gastroscopic study. This conclusion was challenged independently by both Paul[32] and Caravati[6] who in a gastroscopic examination of a large number of subjects found salicylates to have little irritating effect on the gastric mucosa. The technique of the latter investigators differed somewhat from that of Lintott and Douthwaite, which may explain the discrepancy of results.

Muir and Cassar[31] gave insoluble aspirin prior to gastrectomy to patients with peptic ulcers. A gastritis was found in the resected specimen in 12 of 20 cases, whereas in the control series only 2 instances of gastritis were found. The erosion was most marked on the lesser curvature of the stomach in the pyloric region. This finding is of interest, in that Case 3 of this report had a small shallow ulcer and some gastritis in this area. Also Martini[29] reported a patient in whom frequent episodes of melena followed salicylate therapy and who finally developed a demonstrable prepyloric ulcer after a prolonged period of sodium salicylate therapy.

Further evidence that aspirin has a local irritating effect are the presence of blood-stained mucus in the gastric aspirate of patients with peptic ulcer immediately following salicylate ingestion, and an increase in the occult fecal blood of these subjects.

Honigsberger[19] suggested that gastrointestinal hemorrhage may be an allergic response to salicylates rather than one of irritation. He reported 2 cases in which epistaxis could be induced at will by the ingestion of a small amount of aspirin. As stated earlier, Warthin[41] suggested gastric allergy to salicylates as a cause of gastrointestinal hemorrhage. That local tissue sensitivity is possible was demonstrated by Walzer *et al.*[40], who injected human serum bearing a reagin into various sites of the gastrointestinal mucosa of monkeys. Injection of the specific antigen into these animals was followed in 10 minutes by a marked hyperemia and edema of the previously sensitized sites. After 45 minutes the reaction subsided, but in no instancee was there progression to ulceration. Ulcers due to allergic insult have been produced both in the stomach and duodenum of dogs by Friesen *et al.*[11]. These investigators injected horse serum containing five specific antibodies into the submucosa of the stomach and duodenum or directly injected the serum into the arteries supplying these areas. A sustained allergic reaction was produced by the intravenous administration each day of one of the five specific antigens. Hemorrhage regularly occurred and occasionally ulceration. If histamine in beeswax was added to the above procedure, ulceration regularly occurred. Hayashi and Kato[17] produced gastric ulcers with a tendency to chronicity in guinea pigs by repeated allergic shocks.

According to the survey of Gardner and Blanton[12] it would appear that aspirin is not a particularly allergogenic drug. For example, allergy to quinine is seventeen times more frequent than that to aspirin when considered per dose, but because of the tremendous amount of salicylate consumed each year, it assumes great importance. Gross and Greenberg[15] stated that ten million pounds of salicylate compounds were produced in the U. S. A. in 1944.

Although true hypersensitivity of the mucosa to aspirin probably does occur, another mechanism is perhaps operative more frequently in these patients who bleed from the gastroduodenal mucosa after ingestion of aspirin. This

alternate etiology is based both on animal experiments and observations on humans. Barbour[1] was able to produce gastric ulcerations in rats and dogs with both oral and parenteral administration of salicylates. There is ample confirmation of this in these species and in others[15]. The ulceration and hemorrhage do not seem related to the hypoprothrombinemic effect of salicylate, because bleeding occurred only in the stomach and not elsewhere. It is of great interest that Barbour noted that ulceration with salicylates in rats was difficult to achieve during the months of May and June but quite easy September to April. The mechanism of the ulceration was not fully worked out, but it could not be explained as a result of immediate local gastric irritation, as it also occurred after parenteral administration of the drugs and in the absence of vomiting.

Further light was shed on this problem by the investigation of Ivy and his associates[34], who noted, in normal human subjects, that an increase in the volume and acidity of the gastric juice followed ingestion of 1 to 2 gm. of aspirin. This was also seen in normal dogs. Prolonged daily administration of acetyl salicylic acid resulted in definite augmentation of the gastric secretion. After a month of daily ingestion of aspirin (3 gm.), 2 of 3 dogs developed a gastric ulcer. These investigators demonstrated that this augmentation of the volume and acidity of the gastric juice was not due to a local effect on the parietal cells, since they found a 55% increase in the acidity and a 55% increase in the volume of secretion from isolated Pavlov stomach pouches of dogs over a 3-week period. Caravati[6] demonstrated that salicylic acid is not secreted by the stomach, for he was unable to detect any in the stomach contents of patients with high blood levels of salicylate.

The pharmacologic properties of salicylates mimic in many respects those of cortisone. Hailman[16] has arranged a table demonstrating the points of similarity and difference of these substances. Many authorities feel that the therapeutic properties of salicylates as a class are due to cortisone which is released into the blood after stimulation of the pituitary-adrenal system by salicylates. Experimental studies have demonstrated the need of an intact pituitary before salicylates can reduce the blood eosinophils, the cholesterol and the ascorbic acid content of the adrenal cortex, and increase the reducing steroids in the urine[3,9,18,24,33,38,39]. Indeed a case of Cushing's syndrome secondary to high doses of aspirin has been reported[7]. Other investigations have failed to confirm some of these findings[2,37] so the matter is still in dispute. The pros and cons of the situation have ably been discussed by Smith[36] in a recent review. It seems fair to state that salicylates do stimulate the pituitary-adrenal system with the release of adrenal steroids and that the higher the dose, the greater the effect on the adrenal. In spite of this, the weight of evidence suggests that the majority of the effects of salicylates are due to intrinsic properties of salicylates as a class rather than due to increased excretion of adrenal steroids.

Both ACTH and cortisone may reactivate a peptic ulcer or produce an ulcer *de novo*[27]. Both of these substances have been shown to cause an increase in the production of gastric acidity. This may be the explanation either in full or in part of the ulcers complicating therapy with these drugs[13,42]. Indeed, Gray[14] and his associates feel strongly that peptic ulcer activation results from stimulation of the "pituitary-adrenal gastric mucosa

axis" with an increase in gastric acidity and pepsinogen production.

There are numerous clinical reports of the complications of steroid therapy of rheumatoid arthritis by a peptic ulcer. In a discussion of this phenomenon, Bollet and his associates[4] estimated that 7.5% of subjects with rheumatoid arthritis develop a peptic ulcer at some time during steroid therapy. Before the advent of cortisone, the incidence of peptic ulcer in patients with rheumatoid arthritis varied between 4.5 and 8%, which is much higher than would be found in the general population. This is suggestive that salicylates may have been responsible for the increased incidence of ulcer or bleeding in this group, as salicylates were the therapeutic mainstay of most regimens for this disorder prior to 1948. Many of our patients who bled after aspirin were taking this substance for the relief of arthritis.

It is interesting that most drugs effective in relieving arthritis have caused gastrointestinal lesions and hemorrhage. Years ago, cinchophen was abandoned by clinicians mainly because of its toxicity to the liver, but also because of gastrointestinal hemorrhage. Indeed, cinchophen has been used as an experimental tool for the production of gastroduodenal ulcers in laboratory animals[22].

Gastrointestinal ulcers and hemorrhage have been reported with phenylbutazone (butazolidin) which is another potent antirheumatic drug. The mechanism of the formation of peptic ulcer which sometimes complicates the use of this drug has received the attention of Kirsner and Ford[26]. These authors demonstrated very nicely that phenylbutazone will increase the excretion of gastric acid with oral doses within the therapeutic range of this drug. This increase in gastric acidity was not accompanied by a drop in the blood eosinophils. Furthermore, adrenalectomized patients responded to this drug with the same increase in gastric acidity as did the normal subjects. Therefore an intact adrenal cortex is not necessary for this effect. This is of interest because phenylbutazone has many points of similarity with cortisone[5]. Many clinicians felt that this drug was effective by stimulation of the pituitary adrenal system with the subsequent release of adrenal steroids, although it is now clear that it acts independently of the adrenal cortex[5,25].

Kirsner and Ford[26] further demonstrated in dogs that gastroduodenal lesions regularly occur in dogs upon intramuscular administration of phenylbutazone. These lesions usually develop in the absence of any increase of gastric acidity. Therefore, factors other than ones of local irritation, gastric allergy, or of an increased gastric acidity must be invoked. Perhaps the gastric mucin or the mucus cells may be altered by these agents, but data concerning this point are not available. The gastrointestinal lesions produced in laboratory animals by the parenteral administration of salicylate may be similar to the lesions produced by these investigators.

Salicylates may then cause bleeding from the gastrointestinal tract by several mechanisms operating either singly or in combination. They are: a) through the hypoprothrombinemic effect, b) by local tissue irritation, c) by gastric allergy, d) by an increase in gastric acidity, e) by an effect in the gastric mucus cells or on mucin itself.

It is a well known clinical fact that the frequency of hemorrhage in ulcer patients follows a seasonal curve. The peak occurrence of bleeding coincides with the peak for upper respiratory tract infections and minor illnesses such as the familiar "flu." The therapy of these illnesses is usually rest and aspirin.

Perhaps aspirin may be a large factor in the increased incidence of bleeding during this season operating through the mechanisms discussed above. Seasonal tissue reactivity is certainly also operative, as demonstrated by Barbour, who found that ulcers were difficult to produce in rats during the summer months but quite easy during the remainder of the year. It is also of interest that Ivy[23] noted a seasonal variation in the yield of gastric mucin from the mucosa of hogs. Greater amounts were obtained in the winter months than in the fall and spring months.

It is now apparent from the extensive observations of Muir and Cassar and the additional ones embodied in this report that aspirin should be considered in cases of melena which are associated with a proven peptic ulcer or of those in the acute lesion group. It is incumbent upon the physician to question in great detail the patient with melena concerning the use of salicylates. This may spare the patient future episodes of bleeding, needless operation and perhaps even his life.

Summary. A group of patients are reported who gave evidence of upper gastrointestinal hemorrhage after the ingestion of salicylates. These subjects were similar in that bleeding was painless, free acid was found in the fasting stomach, and no roentgenographic proof of an ulcer was present. Three patients experienced numerous bouts of melena over many years. Aspirin ingestion always preceded the bleeding. Hypoprothrombinemia was not the cause of the bleeding as the prothrombin times were normal in all cases where it was determined and the amount of salicylates taken was inadequate to depress significantly the prothrombin concentration of the blood. Gastric allergy to salicylate may have been responsible for the bleeding in the cases where hemorrhage was frequent over a long period.

The use of salicylates appears to increase the frequency of bleeding in patients with proven peptic ulcers. The mechanism of bleeding both in the patients with proven peptic ulcer and in the other group which was without symptoms or laboratory evidence of peptic ulcer is not clear. A local mucosal factor may be the cause, but it seems more likely that aspirin, by augmenting the gastric acidity, leads to peptic erosion and bleeding. The hypothesis is advanced that seasonal incidence of peptic ulcer activation may be partially explained by the more frequent use of this drug in the "ulcer months."

All patients with upper gastrointestinal hemorrhage should be questioned concerning the use of salicylates or proprietary drugs containing salicylates. This may be a lifesaving measure.

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(Interlingua on page 193)

PHARMACOLOGY OF MECAMYLAMINE*

By Ralph V. Ford, M.D.
CLINICAL ASSISTANT PROFESSOR OF MEDICINE AND PHARMACOLOGY

John C. Madison, M.D.
RESIDENT IN MEDICINE

AND

John H. Moyer, M.D.
ASSOCIATE PROFESSOR OF PHARMACOLOGY AND MEDICINE

WITH THE TECHNICAL ASSISTANCE OF
Sam Kinard

Georgia V. Weller

AND

Bobby J. Estes

(From the Medical Service of the Veterans Administration Hospital and the Departments of Medicine and Pharmacology, Baylor University College of Medicine, Houston, Texas)

Mecamylamine** (Fig. 1) (Inversine) represents the first therapeutically useful ganglionic blocking agent that is not a quarternary ammonium compound. Like hexamethonium and pentolinium, it blocks the transmission of impulses through the autonomic (sympathetic and parasympathetic) ganglia. Stimulation prior to blockade has not been observed. The duration of the ganglionic blockade has been shown experimentally to be 10 to 20 times longer than that with hexamethonium and 3 to 4 times longer than that produced by pentolinium[7]. The purpose of this paper is to present the observations of the pharmacologic effects of mecamylamine in the experimental animal (dog) as well as in human hypertensive patients.

Materials and Methods. 1. LABORATORY OBSERVATIONS. *A. Observations on Site of Action.* Seventeen dogs were observed to determine the site of action of mecamylamine (Inversine) when given parenterally in progressively increasing dosages beginning with .05 mg./kg. and increasing to 0.5, 1, and 2 mg./kg. Effects of stimulation of the distal end of the vagus nerve after increasing doses were undertaken in order to determine parasympathetic ganglionic blockade. The blood pressure response to carotid occlusion was also observed in order to determine the effect on vasoconstrictor impulses mediated over the sympathetic nerves.

B. The Blood Pressure Response Curve. The response to increasing doses of mecamylamine was observed and compared to hexamethonium in terms of onset and duration of action. Observations consisted of several control blood pressure readings followed by readings at 15-minute intervals for 5 hours. The drug was given intravenously as a single dose.

C. Renal Studies. The effects on renal clearances of para-aminohippurate (PAH) and creatinine as well as on water and electrolytes (Na and K) were also observed in these dogs[5]. By using increasingly larger doses, 6 dogs were subjected to only mild blood pressure reduction while 11 were subjected to moderate or marked reduction of blood pres-

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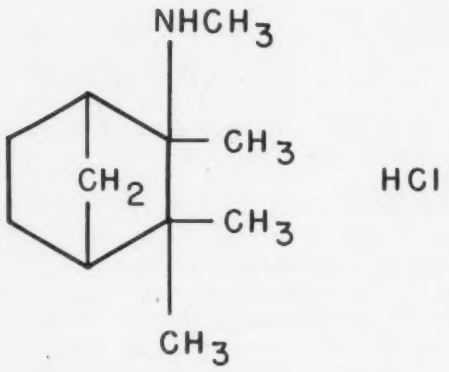
**Available as Inversine from Sharp & Dohme Division of Merck & Co., Inc., West Point, Pa.

sure following parenteral administration of the drug. Two or more 10-minute observations were made in four periods: Control, 1/3, 1, and 3 hours after the administration of the drug.

II. CLINICAL OBSERVATIONS. The observations of the pharmacologic effects in human hypertensives were made on 55 patients (one female, 54 males), most of whom were on an ambulatory outpatient basis, but 19 of these patients were hospitalized in order to more closely observe certain features of the drug. They were maintained on the Renal-Vascular Disease Ward and the observations were made by the investigators, consisting of the authors, nurses, and trained technicians. All patients were fed a diet containing 800 mg. sodium and they were also given 3000 ml. of distilled water per day. The patients had essential hypertensive vascular disease associated with many complications including arteriosclerotic heart disease, cerebral vascular disease, and arteriolar nephrosclerosis. The fundi were classified according to the Keith-Barker-Wagener classification and 14 patients were grade I, 29 were grade II, 8 were grade III, and 4 were grade IV. Renal disease was classified according to previous definitions[3] and 12 patients had no renal disease, 23 were grade I, 11 were grade II, 8 were grade III, and 1 was grade IV. The patients were checked by the usual techniques at monthly intervals (electrocardiogram, chest roentgenogram, phenolsulphonphthalein excretion, Fishberg concentration, urinalysis, hemogram, and blood urea nitrogen).

Blood pressures were checked on the hospitalized patients, during the control period of several days, four times daily in the recumbent and upright positions. After the drug was administered either orally or parenterally, the blood pressure was recorded at 15-minute intervals for 2 hours, then every 4 hours. Those patients who were studied as ambulatory outpatients were observed twice weekly and similar determinations were made.

'INVERSINE'



$C_{11}H_{21}N \cdot HCl$ M. W. 203.8

Fig. 1.—Mecamylamine (Inversine) structural formula.

A. Absorption and Tolerance. In order to determine the degree of absorption of mecamylamine, the drug was given intramuscularly to the hospitalized patients in progressively increasing dosages until a significant orthostatic reduction in blood pressure was observed. The patient was then allowed to return each time to the control blood

pressure state, following which the drug was given by mouth in a similar fashion* until the significant orthostatic hypotensive response was once more elicited. Such observations were conducted on 11 patients. Data were obtained concerning dose, blood pressure effects, the time of onset of effect, the duration of the effect, and side reactions. The effects of progressively increasing dosages during the initial institution of treatment in these patients have also been observed to illustrate the phenomenon of tolerance.

B. Characteristics of Single Dose Responses. In order to get greater information on the oral use of the drug, it was given to 19 patients who were hospitalized. Observations of dose, blood pressure effects, time of onset, and duration of response were made. The observations were made as described above.

C. Renal Studies. A small group of patients (8), in whom an effective dose of the drug was administered daily for two months or more, were observed by means of differential renal function techniques. Measurements of glomer-

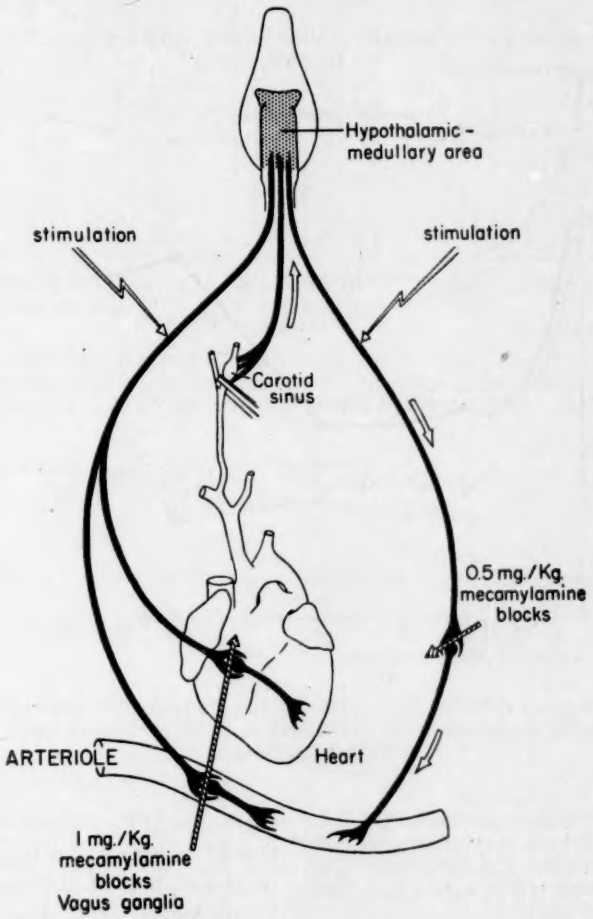


Fig. 2.—Ganglionic blocking action of mecamylamine (Inversine). 1 mg./kg. blocks parasympathetic impulses of distal vagus stimulation and 0.5 mg./kg. blocks sympathetic impulses.

*The first seven patients were studied during a single hospitalization and the control values recorded in Table 1 are an average of 6 to 9 days' readings. The intramuscular dose was progressively increased each day (titration procedure) until the optimal dose was determined. On a subsequent day, the same dose was given orally and the response compared.

ular filtration rate and renal plasma flow as well as the excretion rates of water, sodium, and potassium under these conditions were performed before and after drug administration. Following drug administration, the same studies were repeated in the 45° head-up tilted position. The techniques have been previously described[2,4].

D. Treatment Programs. In an effort to further delineate the pharmacologic attributes of this drug when used clinically, the drug has been given to a large group of outpatients (55) on three different schedules. An effective dose was established by giving the drug once daily, twice daily, and three times daily and the comparative symptomatic effects were observed.

Finally, the results of the clinical use of this drug given to a larger group of outpatients have been compared to previously-reported observations using hexamethonium or pentolinium.

Results. I. LABORATORY OBSERVATIONS. *A. Studies on the Ganglionic Blocking Effects of Mecamylamine (Inversine) in Experimental Dogs.* The effect of parenteral administration of mecamylamine at a dose of 0.5 mg./kg. is illustrated by the blockade of the hypertensive response following carotid occlusion. This suggests blockade of the sympathetic ganglia, although a central effect of the drug has not been ruled out. Blockade of the parasympathetic ganglia (vagus) is illustrated by the blockade of the hypotensive effect of stimulation of the distal end of the vagus nerve at a dose of 1 mg./kg. (Fig. 2).

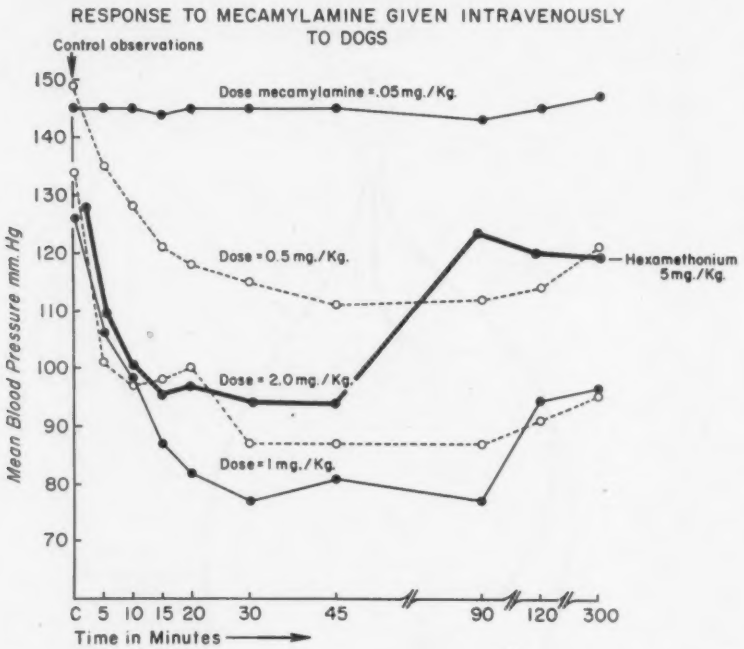


Fig. 3.—Blood pressure response curves. The response to increasing single doses of mecamylamine is compared in magnitude, onset, and duration of blood pressure effect to that produced by hexamethonium.

B. The Blood Pressure Response Curve. The blood pressure response to increasing doses of mecamylamine given intravenously to dogs is demonstrated in Fig. 3. There is no response

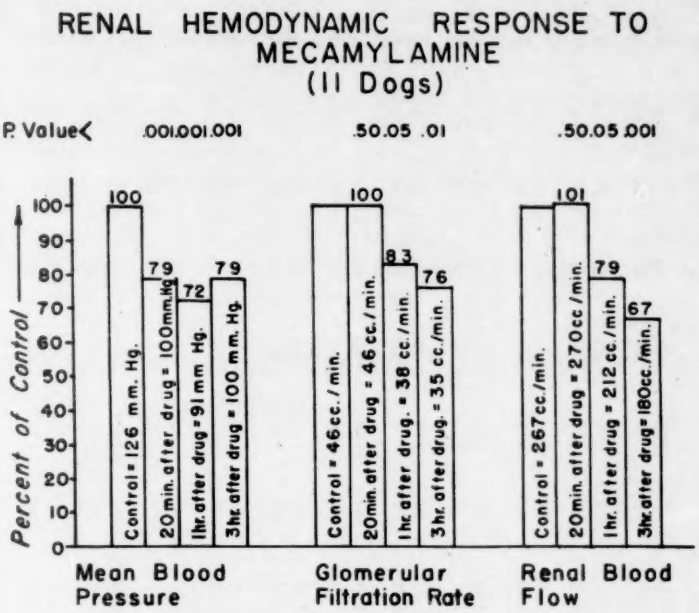


Fig. 4.—Renal hemodynamic response to mecamylamine in dogs. There is an immediate decline in blood pressure (within 20 minutes) without decline in glomerular filtration rate or renal plasma flow until one hour after the drug administration.

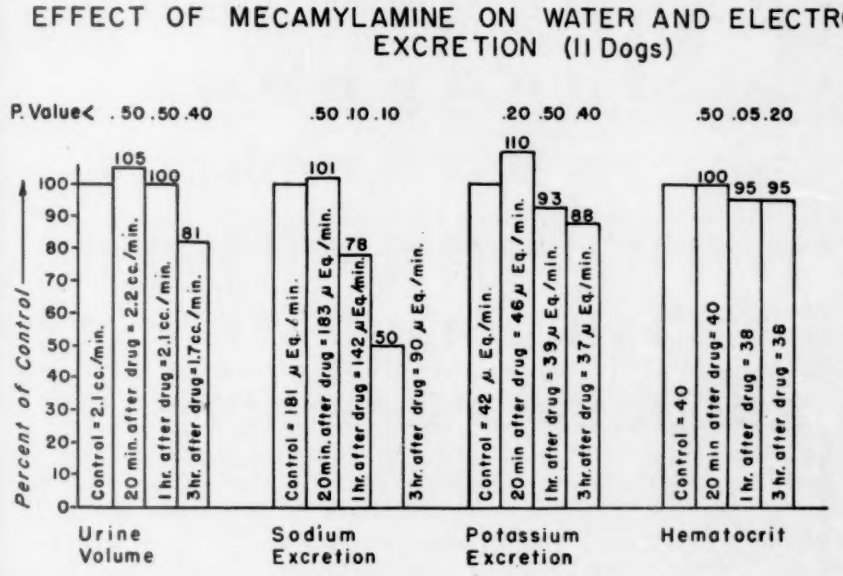


Fig. 5.—Effect on water and electrolyte excretion. There is no statistically significant change.

TABLE 1.—COMPARISON OF THE EFFECTS OF MECAMYLAMINE ADMINISTERED ORALLY AND PARENTERALLY

Patient and Route		Control B.P.*				Drug—Lowest B.P.				Mean B.P. Upright		Onset (min.)	Duration (hrs.)	Dose (mg.)	Side Effects
		Recumbent		Upright		Recumbent		Upright							
		S	D	S	D	S	D	S	D	C	D				
1.	O.C.														
	IM	164	106	144	96	110	70	80	60	112	67	60	8	40	1+
	PO	164	106	144	96	140	90	90	60	112	70	45	12	40	3+
2.	K.A.														
	IM	198	123	178	118	150	90	100	70	138	80	60	12	10	0
	PO	198	123	178	118	160	100	150	90	138	110	45	24	10	0
3.	H.M.														
	IM	228	150	198	148	170	110	150	90	165	110	30	48	20	3+
	PO	228	150	198	148	180	110	120	90	165	100	30	36	20	2+
4.	S.W.														
	IM	208	115	153	100	190	110	100	80	118	87	30	18	15	0
	PO	208	115	153	100	170	110	120	70	118	87	30	18	10	0
5.	M.H.														
	IM	183	103	160	95	140	100	90	70	117	77	15	20	20	0
	PO	183	103	160	95	130	80	100	70	117	80	15	20	20	0
6.	I.D.														
	IM	193	130	155	115	180	110	140	90	128	107	30	16	20	0
	PO	193	130	155	115	170	110	100	70	128	80	30	16	20	0
7.	W.A.														
	IM	200	113	188	123	180	100	140	90	145	107	15	24	10	0
	PO	200	113	188	123	180	100	120	80	145	93	15	24	10	0
8.	S.R.														
	IM	198	137	191	130	132	76	112	82	150	92	30	48	10	1+
	PO	186	138	190	120	138	72	118	78	143	91	60	48	10	1+
9.	T.C.														
	IM	232	144	216	145	187	116	136	106	169	116	90	12	40	0
	PO	250	154	237	148	177	112	144	104	178	117	60	16	40	0
10.	J.M.														
	IM	196	112	188	114	138	78	122	79	115	93	30	12	20	2+
	PO	184	114	186	113	144	87	116	78	137	91	20	15	20	2+
11.	L.T.														
	IM	234	137	223	133	188	105	126	88	163	101	120	18	10	0
	PO	236	138	255	135	223	108	160	100	175	130	60	16	10	0
Average															
	IM	203	125	181	120	160	97	118	82	138	94	46	21	20	
	PO	203	126	186	119	165	98	122	81	141	95	37	22	19	

Legend: S = Systolic, D = Diastolic; C = Control, D = Drug; IM = Intramuscularly, PO = Orally

* The first 7 patients were studied during a single hospitalization and the control values tabulated are an average of six to nine days' readings. The intramuscular dose was given on the first day, the same dose was given orally and the response compared. Consequently, the control values are the same. By contrast, in patients 8 to 11, the optimal dose was

at 0.05/kg. There is a suboptimal response at 0.5 mg./kg. and an optimal response at 1 mg./kg. without significant additional response at 2 mg./kg. The latter responses are roughly equivalent to a dose of hexamethonium of 5 mg./kg. except for duration of action. It will be seen that the 5 mg./kg. dose of hexamethonium has an average duration of 60 minutes while the dose of 2 mg./kg. of mecamylamine has an average duration of action of more than 6 hours.

C. Renal Studies. The renal hemodynamic response to mecamylamine is associated with a prompt decrease in mean blood pressure (within 20 minutes) and at the end of 3 hours is 79% of control. The glomerular filtration rate shows no significant change until 1 to 3 hours after the drug is administered, at which time there is a decrease to 76% of control ($P<.01$). A similar change is seen in renal blood flow, which decreased to 67% of control ($P<.001$) (Fig. 4). The effect of mecamylamine on water and electrolyte excretion is seen in Fig. 5. Although there is a slight decrease in sodium excretion to 50% of control 3 hours after the drug was administered, the significance of this is doubtful. There is no change in urine volume, potassium excretion, or hematocrit.

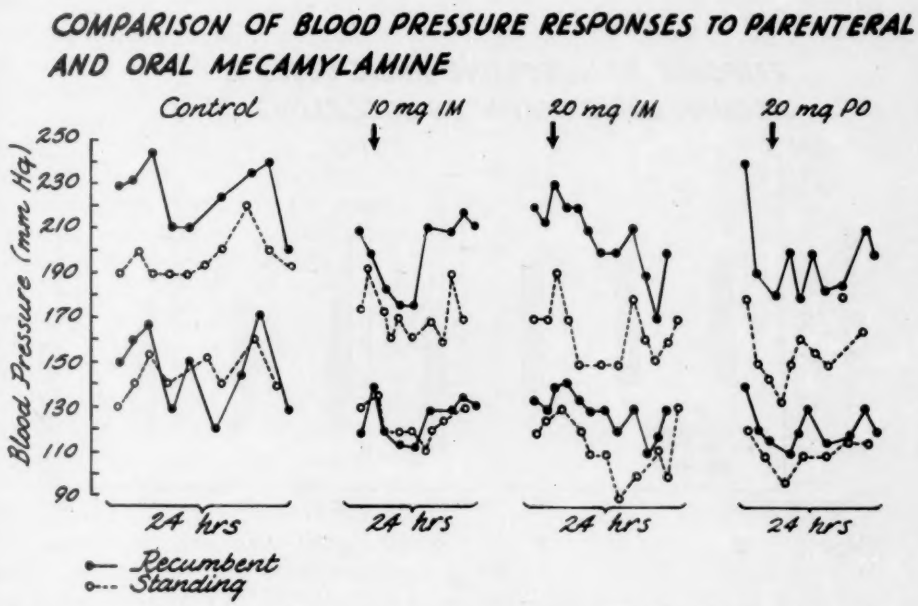
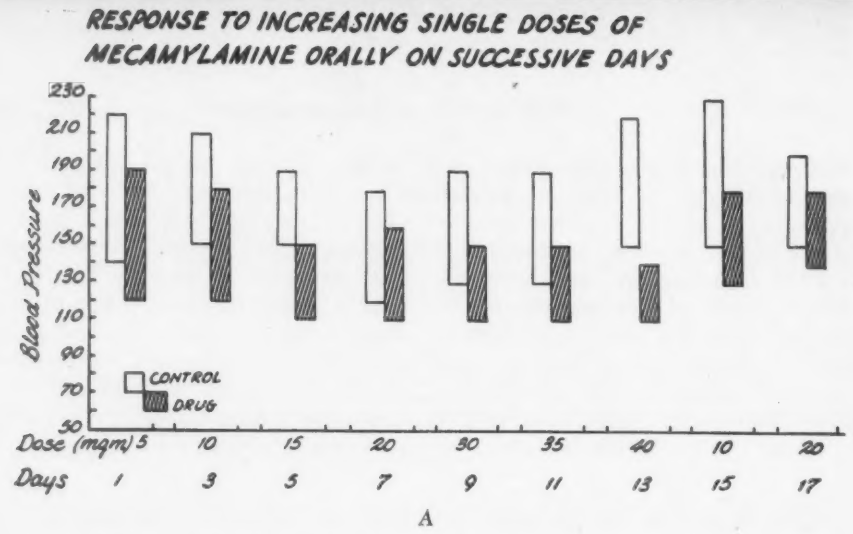


Fig. 6.—Comparison of blood pressure responses to parenteral and oral mecamylamine. The onset and duration of action are similar regardless of method of administration.

II. CLINICAL OBSERVATIONS. *A. Absorption and Tolerance.* The fact of its complete absorption when administered orally is illustrated by comparison of the effects of the drug when given in comparable doses orally as well as parenterally. The mean blood pressure (diastolic pressure plus 1/3 of the pulse pressure) was reduced from a control of 138 (range 112 to 169) to 94 (range 67 to 116) ($P<.001$) following parenteral administration of the drug. A



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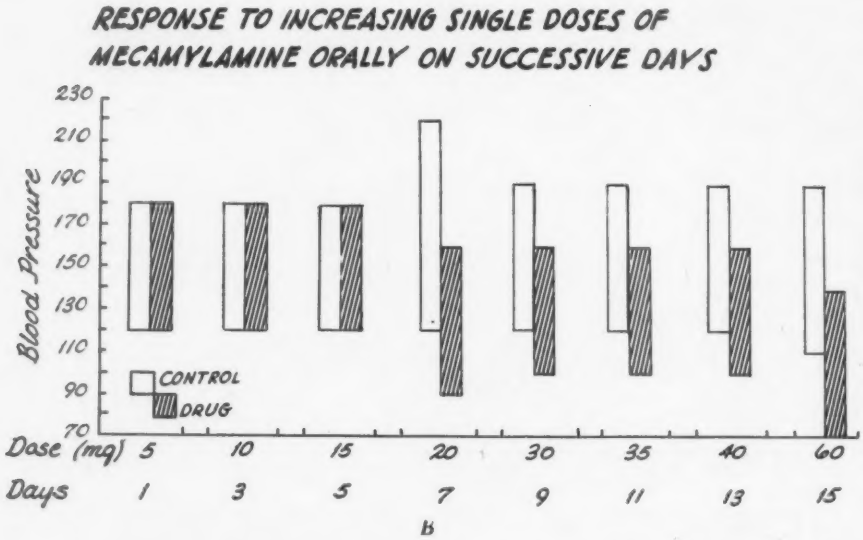

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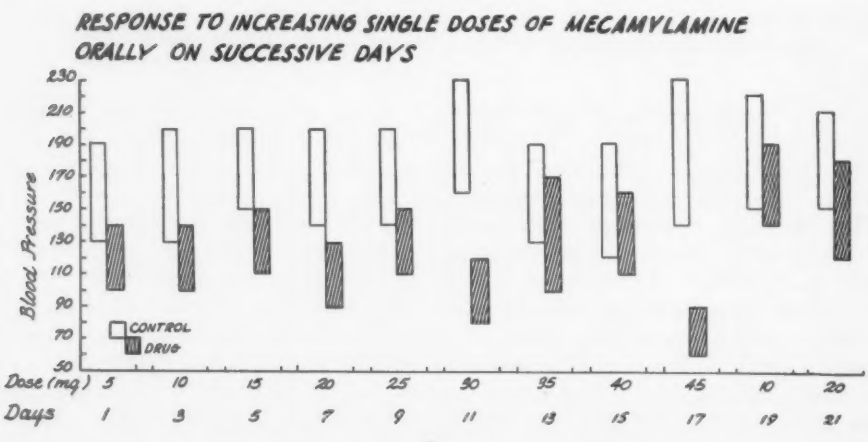

C

Fig. 7.—Response to increasing doses of mecamylamine on successive days. The problem of partial tolerance (initial increase in dose requirement which is not progressive) is illustrated at the 35-mg. dose in Fig. 7*A*; at the 30, 35, and 40 mg. doses in Fig. 7*B*; and at the 35 and 40 mg. doses in Fig. 7*C*.

similar response was elicited when the drug was given by mouth. The average onset of action of the drug was 46 (range 15 to 120) minutes when given intramuscularly and 37 (range 15 to 60) minutes when given by mouth. The duration was 21 (range 8 to 48) hours parenterally and 22 (range 12 to 48) hours orally. The dose was 20 and 19 mg. (range 10 to 40) respectively and the side effects were roughly similar. A typical response is seen in Fig. 6.

The problem of tolerance is illustrated by a small group of patients observed very closely in the hospital while receiving the drug in progressively increasing dosage. Typical examples are presented in Figs. 7*A* to 7*C*. The patient represented in Fig. 7*A* presented good hypotensive responses at progressively increasing doses. However, on administering the 20-mg. dose again, there is less of a response than previously seen. The patient is thus in a phase of partial tolerance to the drug. In Fig. 7*B*, there is no additional effect accompanying an increasingly larger single dose of mecamylamine up to 40 mg. However, when a dose of 60 mg. is administered, there is an additional hypotensive effect noted. The patient thus developed partial tolerance but continued to be responsive at a larger dose. Figure 7*C* illustrates the appearance of partial tolerance at the 35 to 40-mg. dose, which is exceeded at the 45-mg. dose. Upon returning to the 10-mg. dose, which previously produced a quite significant orthostatic response, no significant blood pressure reduction was seen, which is also true of the 20-mg. dose. However, this effect of partial tolerance was overcome by a second "titration" of the drug. Frequently the dose requirement later decreased slightly after the blood pressure was regulated for a prolonged period of time.

B. Characteristics of Single Dose Responses. In order to evaluate the effect

TABLE 2.—THE EFFECTS OF SINGLE DOSES OF ORALLY ADMINISTERED MECAMYLAMINE ON BLOOD PRESSURE

(19 PATIENTS)

	Control				*Drug*							
	Recumbent		*Upright*		*Recumbent*		*Upright*		*Mean Blood Pressure Upright*	
	S	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*Control*	*Drug*
Average	214	132	198	118	173	104	126	79	143	95
Range	170–250	90–140	160–245	90–150	120–230	70–140	70–210	50–120	113–168	57–143
P Value <										.001

	Onset (min.)	*Duration (hours)*		*Dose (mg.)*
		Complete	*Partial*	
Average	68	17	29	13.5
Range	15–120	10–72	18–48	5–40

of single doses of the drug, a larger group (19) of patients was used. The control blood pressures averaged 214/122 in a recumbent position and 198/118 in the upright position. After the drug was administered, the average blood pressure was 173/104 in the recumbent position and 126/79 in the upright position, illustrating a predominant orthostatic hypotensive effect (Table 2). This results in the calculated mean blood pressure reduction from 143 in the control state to 95 after the drug was administered with an average onset of 68 minutes and an average duration of 17 hours for complete control of blood pressure but an additional intermittent blood pressure reduction for a total of 29 hours. The average dose was 13.5 mg. in the small group of patients studied.

C. Renal Studies. In the recumbent position, the patients exhibited a moderate decline in blood pressure (MBP 154 to 135) after 2 months of oral mecamylamine therapy and there was no statistically significant change in glomerular filtration rate (decrease from 80 to 68 or to 85% of control) or renal plasma flow (decrease from 506 to 451 or to 89% of control) for the group. Occasionally an individual patient showed a significant reduction in glomerular filtration rate and renal blood flow which was associated with a significant reduction in blood pressure. In the upright tilted position, after having received mecamylamine for 2 months or more, the patients exhibited a rather marked reduction in blood pressure (to 81% of control) accompanied by a decline in glomerular filtration rate to 74% of control, both of which were statistically significant changes from the post drug supine observations. There was no significant change (due to the drug) in water or plasma electrolytes in the recumbent position compared to the control. Comparing the tilted position to the recumbent position after drug administration, there was no significant change in plasma sodium or potassium. The urine volume decreased to 48% of the post drug recumbent value while the urinary excretion of sodium decreased to 47%, and the potassium excretion decreased to 69% of the recumbent value. These alterations due to tilt were statistically significant.

D. Treatment Programs. The larger group of patients was given the drug on three different treatment programs, that is, one, two, and three times daily. When the drug was given once daily (at 9 a.m.), the average dose was 22 mg.; when given twice daily (at 9 a.m. and 9 p.m.), it was 28 mg./24 hours; and, when given thrice daily (9 a.m., 1 p.m., and 5 p.m.), it was 31 mg./24 hours. The percentage of patients achieving blood pressure responsiveness* (reduction in mean blood pressure of 20 mm. Hg or more) was 91, 89, and 87 respectively. The percentage of patients on three different programs that achieved normotensive levels was 69, 74, and 65, respectively. The untoward symptoms were no different on any of the three treatment programs (Table 4).

Discussion. Mecamylamine has been shown to be a potent and specific ganglionic blocking agent possessing an inherent long duration of action. The ganglionic blocking property accounts for its ability to diminish or abolish the vascular effects of peripheral vagal stimulation, of carotid occlusion, and of injected nicotine. The specificity is illustrated by its inability to antagonize the effects of norepinephrine. It is a secondary amine which results in its greater uniformity and certainty of action when orally administered than the currently available quarternary ammo-

*Average for the 24-hour period.

TABLE 3A.—EFFECT OF MECAMYLAMINE ON RENAL HEMODYNAMICS IN THE SUPINE AND UPRIGHT TILTED POSITIONS

TABLE 3A.—EFFECT OF MECAMYLAMINE ON RENAL HEMODYNAMICS IN THE SUPINE AND UPRIGHT TILTED POSITIONS

	Mean Blood Pressure mm. Hg			*Glomerular Filtration Rate ml./min.*			*Renal Plasma Flow ml./min.*			*Renal Blood Flow ml./min.*			*Hematocrit*					*Dose mg./24 hrs.*
Patient	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*C*	D_1	D_2	*Age*	*Sex*	
1. O.H.	165	138	116	101	83	64	417	354	298	732	681	573	43	48	48	46	F	60
2. L.V.	154	148	111	116	106	89	629	494	340	1066	823	576	41	40	41	53	M	70
3. G.P.	173	152	118	40	35	31	185	185	174	319	314	285	42	41	39	60	F	32
4. H.L.	142	122	107	33	34	31	199	141	124	326	210	203	39	33	39	61	M	28
5. J.B.	154	138	118	66	83	60	329	359	264	491	598	419	33	40	37	69	M	30
6. J.G.	163	126	83	95	42	10	486	352	62	810	533	98	40	34	37	73	M	20
7. E.B.	147	125	101	66	60	38	380	540	398	576	806	594	34	33	33	58	F	20
8. B.J.	137	127	115	119	100	76	1422	1185	906	2155	1669	1313	34	29	31	28	F	20
Mean.....	154	135	109	80	68	50	506	451	321	809	704	508	38	37	38	56	M	35
% of control...		88	81‡		85	74‡		89	71‡		87	72‡		97	103‡			
P-value < *....		.001			.20			.30			.30			.50				
P-value < †....			.001			.01			.05			.01			.50			

C = Control D_1 = Recumbent position after drug. D_2 = Tilted head-up position after drug.

* Comparing supine control observations with observations after two months of continuous mecamylamine administration.

† Comparing supine and upright tile after drug.

‡ Post drug supine value used as control for comparison of response to tilt.

TABLE 3B.—EFFECT OF MECAMYLAMINE ON WATER AND ELECTROLYTE EXCRETION IN THE SUPINE AND HEAD-UP TILTED POSITION

	Plasma Sodium mEq./L.			*Plasma Potassium mEq./L.*			*Urine Volume ml./min.*		*Urine Sodium μEq./min.*		*Urine Potassium μEq./min.*	
Patient	*C*	D_1	D_2	*C*	D_1	D_2	D_1	D_2	D_1	D_2	D_1	D_2
1. O.H.	136	141	141	5.2	4.3	4.3	0.7	0.6	138	94	28	22
2. L.V.	137	144	152	4.7	3.7	3.5	10.5	7.0	191	101	28	25
3. G.P.	144	140	137	5.1	5.1	4.7	6.5	3.3	268	116	58	43
4. H.L.	141	139	145	5.1	6.0	5.8	5.4	5.0	678	596	15	17
5. J.B.	154	151	149	4.6	4.0	3.9	1.2	0.7	228	117	31	21
6. J.G.	130	145	145	4.4	4.4	3.6	0.5	0.1	25	3	37	10
7. E.B.	137	145	141	4.0	3.2	2.9	7.2	1.2	602	15	51	25
8. B.J.	135	137	139	5.4	3.6	3.5	11.4	2.5	558	220	43	33
Mean.....	139	143	144	4.8	4.3	4.0	5.4	2.6	336	158	36	25
% of control...		103	101‡		90	93‡		48‡		47‡		69‡
P-value < *....		.20			.30			.05		.05		.05
P-value < †....			.50			.05						

C = Control D_1 = Recumbent position after drug. D_2 = Tilted head-up position after drug.

* Comparing supine control observations with observations after two months of continuous mecamylamine administration.

† Comparing supine and upright tilt after drug.

‡ Post drug supine value used as control for comparison of response to tilt.

nium ganglionic blocking drugs. Most of the side effects observed are due to blockade of both sympathetic and parasympathetic ganglia (constipation and dry mouth). Weakness and fatigue may be due to the mild curare-like effect (this effect of mecamylamine has been shown experimentally to be .08 that of d-tubocurarine)[7]. There is no reflex tachycardia due to acute blood pressure reduction as is seen with adrenergic blockade. The absence of this reflex tachycardia is apparently the result of blockade of the cardio-accelerator reflexes associated with acute blood pressure reduction. Experimentally, mecamylamine has been shown to increase the barbiturate-induced sleeping time in mice and to block nicotine-produced convulsions. Sympathomimetic drugs (norepinephrine, Vasoxyl, Neosynephrine) are effective in reversing hypotension due to mecamylamine[7].

Because of its completeness of action as well as high potency, the drug is associated with reduction in renal hemodynamic functions (glomerular filtration rate and renal blood flow) when dogs are observed over a period of 3 hours, but there is no change in water and electrolyte excretion. This same effect, however, has been observed when a continuous infusion of other ganglionic agents, such as hexamethonium, is used in dogs. It is to be pointed out, on the other hand, that the *acute* response (less than one hour) to a single dose of mecamylamine, hexamethonium, or pendiomide is not accompanied by a reduction in renal hemodynamic functions or the excretion of water or electrolytes (Figs. 8 and 9). Marked reduction in blood pressure for a long period of time is also accompanied by a reduction in glomerular filtration rate and renal plasma flow in the human hypertensive patient (Table 3A), particularly in patients with severe hypertension prior to therapy. This feature would require close clinical observation in a patient with a suboptimal renal function (renal damage), which is especially prevalent in those patients with severe hypertensive disease requiring the use of ganglionic blocking agents. In previous reports[2,8], the long-term use of hexamethonium and pentolinium in ambulatory hypertensive patients has been associated with no decrease in renal hemodynamics. Any differences, therefore, observed with mecamylamine can be accounted for by its longer duration of action. This effect is observed also when hexamethonium is given as a continuous infusion to both man and the experimental animal when the blood pressure is continuously reduced. In this state, the renal hemodynamics are also depressed. In the tilted position (Table 3A) after the administration of the drug, blood pressure decline was associated with a reduction in

TABLE 4.—COMPARISON OF 3 DIFFERENT TREATMENT PROGRAMS OF MECAMYLAMINE (ORAL)

Doses per 24 Hours	*Mg. per 24 Hours*	*Per Cent B.P.R.**	*Per Cent Normotensive*	*Untoward Symptoms*
1	22	91	69	1+
2	28	89	74	1+
3	31	87	65	1+

* Blood Pressure Responsiveness = decline in mean blood pressure greater than 20 mm. of mercury.
Per Cent Normotensive = upright blood pressure less than 150/100.

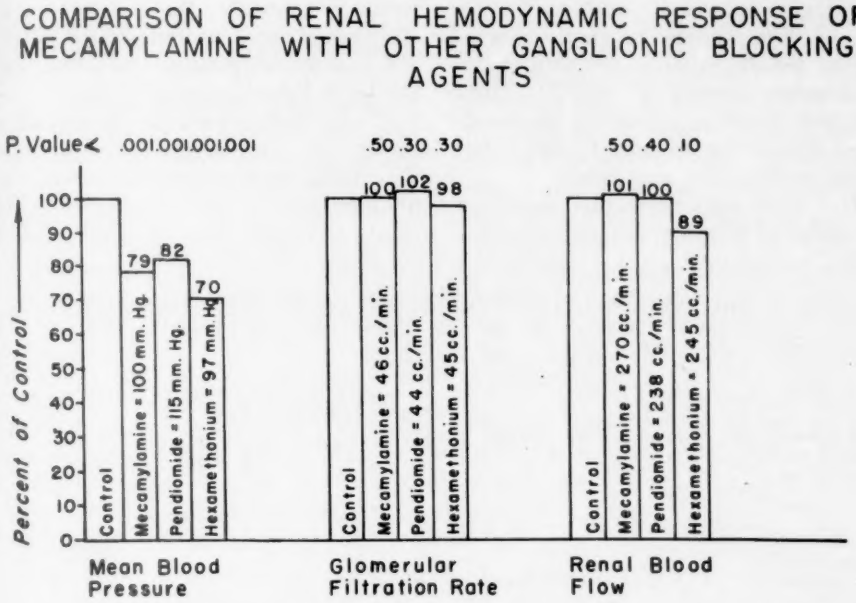

Fig. 8.—Comparison of renal hemodynamic response of mecamylamine with other ganglionic blocking agents. With single injections, the acute changes are similar.

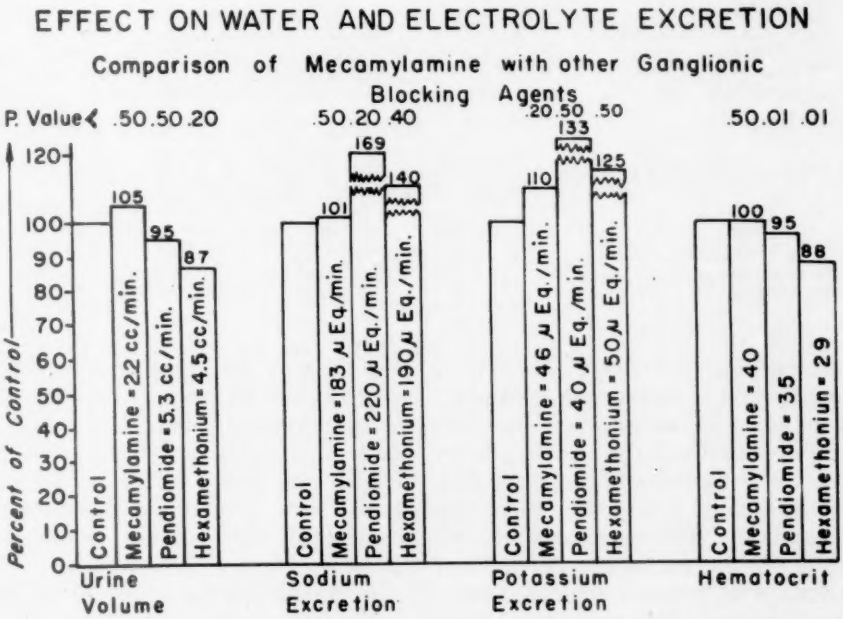

Fig. 9.—Comparison of mecamylamine with other ganglionic blocking agents on the effect on water and electrolyte excretion. There is no significant difference.

glomerular filtration rate and renal plasma flow similar to that observed previously in patients receiving hexamethonium therapy (Table 5). These responses were qualitatively similar to those seen in the untreated patient with hypertension who was tilted[6].

The most important pharmacologic attributes of this drug are its long duration of action (average 17 hours), its prompt onset (average 68 minutes), and its complete absorption when administered orally. In comparing treatment programs consisting of one, two, or three divided doses daily, there was no significant difference between the programs in degree of side reactions or percentage of patients achieving satisfactory control. However, in routine clinical use for the treatment of ambulatory outpatients, the general experience[1] indicates a preference for at least a 3-dose-a-day treatment program with the largest dose given at noon.

The problem of tolerance is an interesting one and is illustrated in other ganglionic blocking agents as well. This phenomenon requires a second "titration procedure" and is illustrated in Fig. 7. It is seen that, in this patient, a small dose was required initially, but, after developing partial tolerance, a dose of roughly two-thirds that previously required (during partial tolerance) was required for satisfactory control of the patient's hypertensive state.

In comparing the effects of the drug in the larger outpatient series of hypertensives at the City-County Hospital,

TABLE 5.—THE MEAN RENAL HEMODYNAMIC RESPONSE TO MECAMYLAMINE COMPARED TO THAT OF HEXAMETHONIUM AND PENTOLINIUM

Drug	*No. of Points*	C_r	D_r	% C_r	*P*val.*	*T*	% D_r	*P'val.*
				Mean Blood Pressure (mm. Hg)*				
Mecamylamine	8	154	135	88	.001	109	81	.001
Hexamethonium	7	159	134	84	.001	104	78	.001
Pentolinium	11	146	118	81	.001			
				Glomerular Filtration Rate (ml./min.)				
Mecamylamine	8	80	68	85	.2	50	74	.01
Hexamethonium	7	73	71	97	.1	56	79	.02
Pentolinium	11	83	80	96	.1			
				Renal Blood Flow (ml./min.)				
Mecamylamine	8	809	704	87	.3	508	72	.01
Hexamethonium	7	801	815	102	.1	501	61	.01
Pentolinium	11	866	963	111	.1			

* Mean Blood Pressure = Diastolic pressure plus one-third of pulse pressure
C_r = Control recumbent
D_r = Drug recumbent
% $C_r = D_r/C_r \times 100$
% $D_r = T_r/D_r \times 100$
P*val. = Comparison of C_r with D_r
T = Tilted head-up position for mecamylamine and ambulatory state for hexamethonium
P' val. = Comparison of D_r with T

TABLE 6.—COMPARISON OF BLOOD PRESSURE RESPONSE TO MECAMYLAMINE, HEXAMETHONIUM AND PENTOLINIUM

Drug	*No. of Pts.*	*Av. Dose (mg.)*	*Responsive*	*Normotensive*
Mecamylamine	81	28	90%	34%
Hexamethonium	75	2307	76%	37%
Pentolinium	75	341	79%	33%

it is seen that the average dose of mecamylamine required to produce significant effects was 28 mg. per 24 hours, while, with hexamethonium, it was 2,307 mg. per 24 hours and, with pentolinium, 341 mg. per 24 hours. The percentage of patients achieving a responsive level was 90, 76, and 79, respectively. Those becoming normotensive were 34, 37, and 33% (Table 6).

Summary and Conclusion. 1. Mecamylamine is a potent ganglionic blocking agent with a long duration of action, which is completely absorbed when administered orally.

2. There is suppression of renal hemodynamics when the drug is administered in doses that produce marked reduction of blood pressure.

3. The agent is the drug of choice in the treatment of moderate to severe hypertensive patients.

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SUMMARIO IN INTERLINGUA

Pharmacologia de Mecamylamina

1. Mecamylamina es un potente agente de blocage ganglionic con action a duration prolongate. Illo es absorbite completemente post administrationes oral.

2. Occurre suppression de hemodynamica renal si le droga es administrate in doses que produce marcate reductiones del pression sanguinee.

3. Le agente es le droga de election in le tractamento de moderate o sever hypertension.

CLINICAL EVALUATION OF A DIGITALIS TOLERANCE TEST

By Robert Gilbert, M.D.
INSTRUCTOR OF MEDICINE

AND

Richard H. Lyons, M.D.
PROFESSOR OF MEDICINE

(From the Department of Medicine, State University of New York Upstate Medical Center at Syracuse, New York, and the Veterans Administration Hospital, Syracuse, New York)

Acetyl strophanthidin is a rapid acting digitalis-like preparation, obtained by esterification of the cardiac aglycone, strophanthidin. Structurally, it is closely related to ouabain (Fig. 1). By present methods of assay, 3 cat units are approximately equal to 0.5 mg. Physiologically, its effect is more rapid than ouabain and much more transitory. Gold[4] has found that after intravenous administration its peak effect is reached in 10 to 15 minutes and the total effect wears off in about 4 hours. Toxicity, when it occurs, usually is gone within one hour[2,6]. Wedd and Blair[7], in experiments with the isolated turtle heart, have postulated that its effect might be due entirely to vagal action; others[5], however, have denied this and feel that acetyl strophanthidin has a true effect on the force of contraction of cardiac muscle. Certainly, from a clinical standpoint, all the reports available indicate that in man it has an action very similar to all other digitalis preparations.

Because of its rapid action and rapid dissipation, Lown and Levine[6] suggested that it be used to determine the degree of digitalization in patients where this was in doubt, and presented the results of 20 cases where acetyl strophanthidin was used in this manner. The present study was undertaken to further evaluate this procedure.

Methods. The test was performed in a manner similar to that outlined by Lown and Levine[6]. Three cat units of acetyl strophanthidin were diluted to 10 ml. with normal saline or 5% dextrose in water. This solution was then administered intravenously at the rate of 1 ml. per minute. A direct writing electrocardiogram was monitored continuously during the procedure and a 1- or 2-minute control strip was obtained before starting the injection. After the first 5 ml. the injection was discontinued for 5 minutes and then restarted at the same rate if no results were noted. If no changes occurred within 10 minutes after the first 3 cat units had been administered, another 3 units were injected in the same manner. For the last 6 cases the test procedure has been modified so that 3 cat units are diluted to 20 ml. and this solution administered at the rate of 1 ml. per minute with a 3-minute pause after each 5 ml. This has not been noted to alter the accuracy of the test and it is felt that it adds to the safety.

The criteria for interpretation are the same as those used by Lown and Levine. If electrocardiographic signs of digitalis toxicity were noted after 1.5 cat units, the patient was considered to be in digitalis intoxication before the test. These signs included ventricular premature beats, bigemini, prolongation of the PR interval, regularization of the rhythm in atrial fibrillation, or any other marked change in rate or rhythm other than simple slowing. If signs of toxicity appeared after 3 cat units the patient was considered adequately digitalized. If a therapeutic effect was noted after 3 or 4.5 units, (as evidenced in our study by a 20% slowing of the heart rate) the patient was considered underdigitalized, and if a therapeutic effect or no effect occurred after 6 cat units, complete redigitalization was advised. In addition to electrocar-

diographic changes, marked nausea or retching was also considered indicative of toxicity.

Results. The digitalis tolerance test was performed 21 times on 18 patients. Almost all were in moderate to severe congestive heart failure and all but 4 had been receiving digitalis up to the time of the test.

On the basis of the test results, there were 7 cases of overdigitalization and 5 of underdigitalization. In 7 cases the patient was considered adequately digitalized and in 2 instances complete redigitalization was advised. In 12 cases the clinical opinion prior to the test was confirmed by the test. In 9 cases the test contradicted the clinical opinion. In 17 cases, follow-up study demonstrated that the test had accurately portrayed the patient's digitalis status. In one case where the test indicated that the patient was adequately digitalized and could be kept on maintenance, digitalis was withheld and the patient improved. Even here, however, the test did answer the most important question in the minds of those caring for the patient, namely, that additional doses of digitalis would be harmful. In 2 cases adequate follow-up could not be obtained. One patient expired during the procedure, very probably as a direct result of the injection.

Illustrative Case Reports. CASE 1. L.B., a 64-year-old woman with arteriosclerotic heart disease and a previous myocardial infarction was admitted to University Hospital because of a fractured hip which was pinned on March 8, 1955. On March 10, 1955, she was noted to be in heart failure, received 1.2 mg. of digitoxin over a 3-day period and was then placed on maintenance of 0.2 mg. per day. She continued to develop increasing heart failure, however, and became lethargic. On April 5, 1955, she received 2 ml. of a mercurial diuretic. Two days later she was noted to have frequent ventricular premature contractions and short runs of ventricular tachycardia. On April 8, 1955, digitoxin was discontinued and she received 2 gm. of potassium chloride by mouth. The premature beats subsided but failure and tachycardia persisted. A digitalis tolerance test was performed 3 days after digitoxin was discontinued. The patient received a total of 6 cat units of

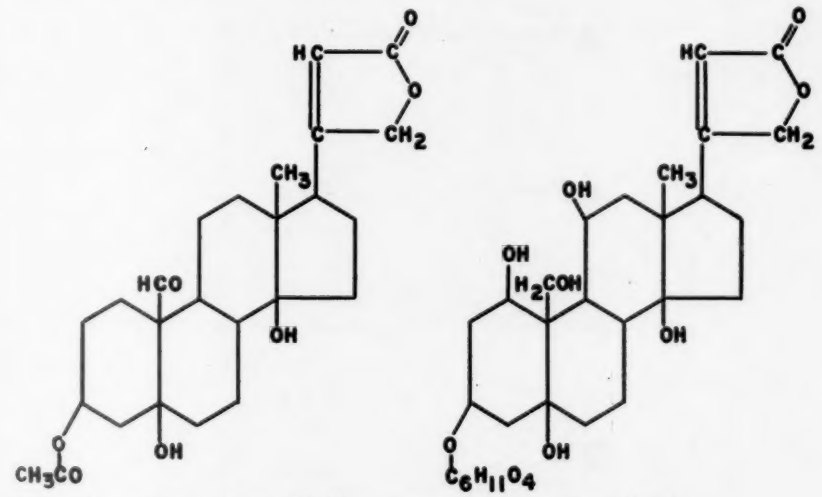

Fig. 1.

acetyl strophanthidin with only a minimal drop in heart rate and no evidence of toxicity. The test indicated that the patient needed complete redigitalization. She then received 1.5 mg. of intramuscular digoxin and was placed on maintenance of 0.75 mg. of oral digoxin per day. With this treatment the heart rate slowed and the patient showed considerable clinical improvement.

CASE 2. A.P. was a 72-year-old man who had hypertensive cardiovascular disease and had been on maintenance digitalis. During the week prior to hospitalization he developed progressive signs of cardiac failure. On admission to University Hospital he was markedly dyspneic and orthopneic, had rales over the entire posterior chest and showed extensive peripheral edema. The electrocardiogram showed a sinus tachycardia with a rate of 116. It was the clinical impression that the patient was underdigitalized but before administering extra digitalis, a digitalis tolerance test was performed. After 3 cat units of acetyl strophanthidin, with no change in rate, the P waves became irregular in size and he showed marked nausea and retching. The injection was stopped and 2 minutes later the patient developed a nodal rhythm (Fig. 2). This persisted for 30 minutes, then briefly changed to a wandering pacemaker and 5 minutes later the electrocardiogram was back to sinus rhythm. The test was interpreted as showing that the patient was already adequately digitalized and should be kept on maintenance. This was done along with the usual measures for heart failure. Several days later the rate had come down to 88 and there was marked clinical improvement. Three weeks later, when the patient was almost ready for discharge, he developed a nodal rhythm similar to that noted during the digitalis tolerance test. Digitalis was discontinued and 11 days later he reverted to sinus rhythm.

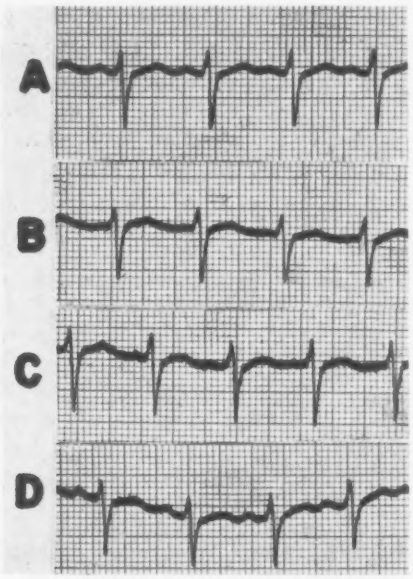

Fig. 2.—Electrocardiograms in Case 2. *A*. Control. *B*. Nodal rhythm after 3 units of acetyl strophanthidin in 15 minutes. *C*. Wandering pacemakers 30 minutes after completion of injection. *D*. Return to control tracing 5 minutes later. All strips are taken on lead III.

Had extra digitalis been administered on admission as was planned, a nodal rhythm might have developed and persisted for many days, along with marked nausea and retching. In view of his critical condition at that time, this could have had a very deleterious effect on his clinical course. The development of nodal rhythm 3 weeks later while on maintenance digitalis, illustrates the fact that although the digitalis tolerance test can

indicate that a patient should be on maintenance digitalis, it cannot predict what that dose should be.

CASE 3. E.C. The patient who expired was a 54-year-old woman with rheumatic heart disease and aortic stenosis who had had repeated episodes of cardiac failure. She entered University Hospital on this occasion in severe congestive heart failure. She was semi-comatose and unable to give a clear history but she apparently had been taking her maintenance dose of digitalis up to the time of admission. When seen she was markedly dyspneic and cyanotic, the heart rate was 100, grossly irregular and the blood pressure unobtainable. There were signs of pleural effusion in the right chest and there was marked peripheral edema. One thousand milliliters of straw colored fluid was removed from the right chest with no clinical improvement. The patient was considered to be in critical condition and it was believed that if she could take more digitalis it might be lifesaving. A digitalis tolerance test was carried out. The control electrocardiogram showed a sinus rhythm, rate 100, PR interval 0.16, and frequent atrial and ventricular premature contractions. The patient received 1.5 cat units of acetyl strophanthidin over a 5-minute period. Two minutes after this injection she

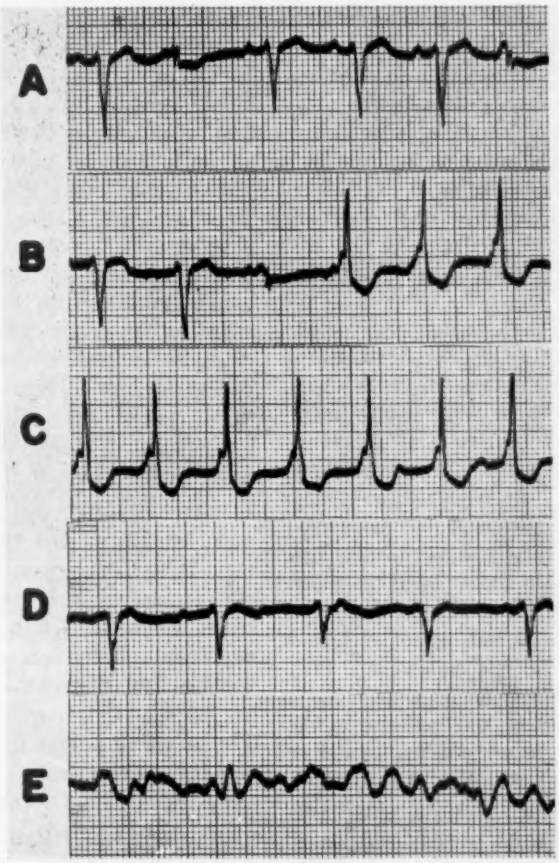

Fig. 3.—Electrocardiograms in Case 3. *A*. Control. *B*. Sudden onset of ventricular tachycardia 2 minutes after completion of injection of 1.5 units of acetyl strophanthidin in 5 minutes. *C*. Persistence of ventricular tachycardia. *D*. Temporary reversion to supraventricular rhythm after intravenous administration of 0.38 gm. of potassium chloride. *E*. Ventricular fibrillation one minute later. All strips are taken on lead III.

suddenly developed ventricular tachycardia (Fig. 3). Potassium chloride was given intravenously and there was a temporary reversion to a supraventricular rhythm. One minute later ventricular fibrillation occurred and the patient quickly expired. Permission for necropsy could not be obtained.

No errors were made in the interpretation of the electrocardiogram and even in retrospect it is felt that the patient was a good candidate for the test. The only thing that might have saved her was slower injection of the drug. As mentioned above, the injection is now being given at half the previous rate, or 0.75 cat units in 5 minutes with a 3-minute wait between each 5-minute injection period. The 3-minute wait was arrived at because it has been noted in our series that if toxicity is to occur, it will almost always develop within 2 minutes of the completion of the injection. This slower method does not seem to alter the accuracy of the test and it is hoped that it will decrease the risk.

Discussion. In reviewing our study and that of Lown and Levine, two facts stand out regarding the digitalis tolerance test with acetyl strophanthidin. These are its accuracy and its great risk. In all but one of our cases where adequate follow-up was obtained, the interpretation of the test had been correct, and even in this one the test fulfilled its function. One possible drawback in interpretation is that the indication of a therapeutic effect is based almost entirely on the heart rate. It is certainly possible that as the drug is being administered the patient could be undergoing more efficient cardiac contractions with an increase in cardiac output without an accompanying drop in the heart rate. At present we know of no way to circumvent this and can only restate the fact that with the present criteria the test has been found to be very accurate. It might be added that we have found acetyl strophanthidin just as effective in slowing the rate in sinus rhythm as in atrial fibrillation.

The test procedure does carry a real hazard. Lown and Levine had 1 fatality in 20 and we have had 1 in 21 trials. This puts the mortality rate at 5%. In addition to this there have been two other deaths reported in the literature from ventricular fibrillation following the injection of acetyl strophanthidin[1,3]. In one of these, however, a total of 6 cat units was administered as a single dose, and in the other 3 cat units. More careful selection of cases for the digitalis tolerance test might eliminate an occasional patient in whom the suspicion of digitalis intoxication might be strong enough to allow foregoing the test. Actually, it is just those patients in whom the test is most indicated who would tend to present the greatest risk because they might not survive even a temporary worsening of their status. Therefore, the test must be viewed in somewhat the same light as one might view a dangerous operation; that is, it should be performed only when it would be more dangerous not to do it. Many cases are seen where digitalis intoxication is suspected but the diagnosis is insecure. In almost all of these cases digitalis can be withheld and the patient observed, time will always give the answer. The digitalis tolerance test is indicated only in those cases where it is felt that the clinical condition of the patient is such that withholding digitalis might be fatal if the patient is not manifesting toxicity. The fact that acetyl strophanthidin will give the answer much more quickly does not justify its use. Again, many cases are seen where underdigitalization is suspected but not proven. Most patients can tolerate mild degrees of digitalis intoxication fairly well and a patient felt to be underdigitalized can be carefully pushed toward toxicity with any

of the standard preparations. It is only the occasional case where even a mild prolonged episode of digitalis intoxication might be disastrous, where the digitalis tolerance test is indicated.

Summary and Conclusions. A digitalis tolerance test utilizing the rapid acting preparation acetyl strophanthidin was employed in 21 cases where the status of digitalization was in doubt. Basically, the test involves administering the drug until either a therapeutic or toxic effect is noted. Follow-up study showed the interpretation of the test to be very reliable. There was one fatality associated with the procedure. It is concluded that the digitalis tolerance test with acetyl strophanthidin is very accurate but hazardous, is needed only rarely, but where indicated can give valuable and often lifesaving information.

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SUMMARIO IN INTERLINGUA

Evalutation Clinic de un Test de Toleration de Digitalis

Un test de toleration de digitalis per medio del preparato a action rapide, acetyl-strophanthidina, esseva empleate in 21 casos in que le stato de digitalisation esseva dubitose. In principio le test se executa per administrar le droga usque un effecto therapeutic o toxic es notate. Un studio subsequential monstrava que le interpretation del test esseva multo digne de confidentia. Un caso mortal esseva associate con le procedimento. Nos conclude que le test de toleration de digitalis per medio de acetyl-strophanthidina es multo exacte sed hasardose. Illo es requirite infrequentemente, sed in casos in que illo es indicate, illo pote revelar informationes de valor e assi forsan devenir un factor decisive in salvar le vita del patiente.

QUANTITATION OF THE MANIFESTATIONS OF RHEUMATOID ARTHRITIS

4. AREA OF JOINT SURFACES AS AN INDEX TO TOTAL JOINT INFLAMMATION AND DEFORMITY

By John Lansbury, M.D.
PROFESSOR OF CLINICAL MEDICINE

AND

Donald D. Haut, A.B.

(From the Departments of Medicine and Anatomy, Temple University School of Medicine, Philadelphia, Pennsylvania)

In evaluating the over-all status of a patient with rheumatoid arthritis we unconsciously make an estimate of the total amount of joint involvement or "spread" of the disease. But we lack a standard method for quantitating this and expressing it as a simple grade or percentile figure. The purpose of this paper is to present some data on which an objective summation of total joint involvement may be based and to explore possible applications of such data to the quantitative evaluation of the activity and deformity in cases of rheumatoid arthritis.

Other things being equal, a patient whose arthritis involves ten of his peripheral joints is obviously worse off than is a patient with involvement of only two of his peripheral joints. But, a simple count of the number of affected joints does not give us a reliable picture of his status; for a patient whose both knees are involved obviously has a greater "amount" of arthritis than he would have if only two knuckles were involved. Clearly, the *size* of the affected joints must be taken into consideration. Our first step in estimating total articular involvement must, therefore, be to find a satisfactory index of joint size.

DETERMINATION OF JOINT SIZE. From the point of view of normal anatomy, it is reasonably easy to find a satisfactory definition of joint size. However, from the point of view of the pathology of rheumatoid arthritis, the matter is considerably more complicated, for we are dealing with an exceedingly variable involvement of structures both within and without the joint capsule. Thus, even in early cases, Roentgen ray may demonstrate rarefaction of the component bone ends and physical examination may indicate involvement of many of the attending structures such as bursae, tendon sheaths, muscles and others. On the other hand, the process may remain for long periods within the joint capsule without obviously affecting these surrounding structures.

After exploring various kinds of joint measurement we have come to the conclusion that the area of the bony surfaces, which in life are covered with cartilage to form the articulating surfaces, is the most satisfactory index of joint size. Although it does not actually take into account all the various tissues which may be involved in the rheumatoid process, it is *proportional to these*. It must be emphasized that although joint surfaces are an important site of

early rheumatoid lesions, we are dealing with these surfaces only as an *index to joint size* and we are *in no way* trying to measure the extent of the lesions on these same surfaces. Since the histological details of joint involvement can never be known in life, we must make our estimate of joint inflammation and impaired function on clinical rather than pathological grounds. For summing up such information joint surface seems quite satisfactory as an index to joint size.

METHOD OF MEASURING JOINT SURFACES. Having chosen the area of the component bone ends of the peripheral joints as a basis for estimating joint size, we measured these by applying aluminium foil with meticulous care to the surface which in life is covered with articulating cartilage. The resulting mold, which was free of wrinkles, was then weighed several times, and its average value to the second decimal place noted. The surface area was then calculated in square centimeters by referring to the weight of a standard square centimeter of the foil used. Our study was performed on one skeleton only, but we think that the values which we obtained may safely be applied to any human skeleton, since variations in *relative* joint size which might occur in different types of body build would almost certainly not be sufficient to vitiate our norms at the level of clinical application.

The peculiar anatomy of certain joints calls for special consideration. Thus, in the case of the knee, we have elected to include the patellar surface; in the case of the shoulder, we have expanded the shallow area of the glenoid fossa by including the surface of the glenoid ligament; and in the case of the sternoclavicular and temporomandibular joints, which are each divided into two separate cavities by an articular disk, we have disregarded the area of the disk. The complicated mosaic of the small carpal and tarsal bones presents a peculiarly difficult problem. Although these areas are frequently involved in the rheumatoid process, it is exceedingly hard, if not impossible, to judge the location and extent of such involvement; furthermore, there is very little motion between the component bones, so that an estimate of joint size based on a total of all their articulating facets would be disproportional to the clinical findings of arthritis in this area. We have, therefore, rather arbitrarily taken into consideration only the transverse articulating surfaces of these areas. A different treatment of the above controversial areas would not appreciably alter our clinical estimate of the "spread" of the disease.

Our measurements of the joint surfaces in one upper and one lower extremity are presented in Table 1. It will be noted that the total area of the joint surfaces amounts to approximately one square meter. This is a fortunate mathematical accident which permits us to express the percentage value of each joint by simply moving a decimal point, thus avoiding tedious calculations.

ESTIMATING THE SPREAD OF THE DISEASE. For practical application, the values given in Table 1 have been reduced to whole numbers and are presented in Table 2. Further mathematical streamlining could be undertaken. Thus, the average value for the proximal interphalangeal, metacarpophalangeal and carpometacarpal joints taken together is 4 cm.^{2}, and no serious discrepancy would result if one took the figure 4 to represent any one of these joints. More radical simplifications could be introduced, but only at the cost of increasing error. In practice we

have found it easy to memorize the values for the commonly involved joints as given in Table 2.

To determine the "spread" of the disease, one takes into account all the peripheral joints which present any symptom or sign of inflammation or of loss of motion due to past (inactive) disease. The percentage of joint morbidity in relation to total possible joint involvement is determined by recording the values for each affected joint, as given in Table 2, adding them and placing a decimal point before the last digit. This takes no more time than does writing out the name of each individual joint which has been affected.

TABLE 1.—AREA OF BONY SURFACES COMPOSING INDIVIDUAL JOINTS

Joint—Upper Extremity	*Digit*	*Observed Area*
Terminal interphalangeal	# 2	1.36 cm.²
Terminal interphalangeal	# 3	1.82 cm.²
Terminal interphalangeal	# 4	1.35 cm.²
Terminal interphalangeal	# 5	1.01 cm.²
Proximal interphalangeal	# 1	2.79 cm.²
Proximal interphalangeal	# 2	2.54 cm.²
Proximal interphalangeal	# 3	3.04 cm.²
Proximal interphalangeal	# 4	2.65 cm.²
Proximal interphalangeal	# 5	2.44 cm.²
Metacarpophalangeal	# 1	5.29 cm.²
Metacarpophalangeal	# 2	5.34 cm.²
Metacarpophalangeal	# 3	6.33 cm.²
Metacarpophalangeal	# 4	5.15 cm.²
Metacarpophalangeal	# 5	5.06 cm.²
Carpometacarpals, Nos. 1, 2, 3, 4, 5 (average 4.41 cm.² each)		22.09 cm.²
Transverse intercarpals		14.92 cm.²
Wrist (radio-ulnar carpal)		14.67 cm.²
Elbow (radio-ulnar humeral)		52.05 cm.²
Shoulder (humeroscapular)		45.17 cm.²
Acromioclavicular		4.05 cm.²
Sternoclavicular		11.91 cm.²
Temporomandibular		3.95 cm.²
		214.98 cm.²

Joint—Lower Extremity	*Digit*	*Observed Area*
Terminal interphalangeal	# 2	0.72 cm.²
Terminal interphalangeal	# 3	0.65 cm.²
Terminal interphalangeal	# 4	0.51 cm.²
Terminal interphalangeal	# 5	0.39 cm.²
Proximal interphalangeal	# 1	3.19 cm.²
Proximal interphalangeal	# 2	1.42 cm.²
Proximal interphalangeal	# 3	1.11 cm.²
Proximal interphalangeal	# 4	0.95 cm.²
Proximal interphalangeal	# 5	0.85 cm.²
Metatarsophalangeal	# 1	8.49 cm.²
Metatarsophalangeal	# 2	4.38 cm.²
Metatarsophalangeal	# 3	3.61 cm.²
Metatarsophalangeal	# 4	3.51 cm.²
Metatarsophalangeal	# 5	3.27 cm.²
Tarsometatarsal joints		24.80 cm.²
Transverse intertarsals		11.55 cm.²
Talonavicular-calcaneocuboid		21.07 cm.²
Talocalcaneal (subastragalar)		18.51 cm.²
Ankle (talus-tibia-fibula)		35.11 cm.²
Knee and patella		103.78 cm.²
Hip		82.52 cm.²
		330.39 cm.²

Total bone-end surface of peripheral joints = 214.98 + 330.39 × 2 = 1090.74 cm.²

TABLE 2.—VALUES FOR INDIVIDUAL JOINTS EXPRESSED IN WHOLE NUMBERS FOR CALCULATING TOTAL AMOUNT OF JOINT INVOLVEMENT IN RHEUMATOID ARTHRITIS.

Upper Extremity	
Each terminal interphalangeal joint	1
Each proximal interphalangeal joint	2
Each metacarpophalangeal joint	5
Each carpometacarpal joint	4
Transverse intercarpal joint area	15
Wrist	15
Elbow	52
Shoulder	45
Acromioclavicular	4
Sternoclavicular	12
Temporomandibular	4

Lower Extremity	
Each terminal interphalangeal joint	0.5
First proximal interphalangeal joint	3
Remaining proximal interphalangeal joints	1
First metatarsophalangeal joint	8
Remaining metatarsophalangeal joints	5
Tarsometatarsal joint area	25
Transverse intertarsal joint area	12
Talonavicular-calcaneocuboid	21
Talocalcaneal (subastragalar)	18
Ankle	35
Knee with patella	104
Hip	82

To determine percentage of total joint involvement, add up the values for each affected joint, place a decimal point before the last digit of the total figure.

With a little more effort it is possible to take into account the extent of both active disease and of deformity. For this purpose a suitable end-point for "active disease" would be tenderness or pain on active motion and for "deformity," any significant restriction of motion. These are qualitative rather than quantitative end-points, and are designed to detect minimal rather than maximal degrees of joint involvement. A further qualitative end-point would be fibrous or bony ankylosis. A summation of these findings may again be obtained from Table 2. The following brief case abstracts illustrate the *kind* of information which the method provides (Table 3). We emphasize that, so far, we are only indicating the *spread* of inflammation and of deformity and *not* taking into account the severity of these.

In relatively early cases, the "spread" of the disease will be the same as the figure for active disease, and the figure for deformity will be less. In chronic cases the percentage of deformity (restricted motion) will be the greater. Except in unusual cases where residual joint thickening is present without pain, tenderness or restricted motion, the highest figure for either activity or deformity will equal the spread of the disease. We have found this type of summation useful as part of the record of the status of new patients. It may also be used to detect slowly occurring changes at intervals of several months.

SUMMATION OF DEGREES OF JOINT INFLAMMATION AND DEFORMITY. When degrees of inflammation and of deformity are taken into account, we leave behind the simple evaluation of the spread of the disease, which was our primary objective, and move, with some reluctance, into a new and much more complex field in which we are really quantitating the "stage" of the disease from a clinical point of view. Such valuable, quantitative information can only be purchased at the heavy price of much time-consuming, meticulous effort required by *any* reliable evaluation of joint findings.

TABLE 3.—APPLICATION OF AREA OF JOINT SURFACES AS INDEX TO TOTAL INVOLVEMENT AND DEFORMITY

Patient Data	*Spread*	*Active Disease*	*Restricted Motion*
Miss B., aged 27. Joints involved: Both 4th proximal interphalangeals and 5th right. Both terminal thumb joints.	1%	1%	0%
Mr. T., aged 50. Joints involved: Both wrists, right elbow and ankle. Right 3rd metacarpophalangeal	12%	12%	12%
Mrs. K., aged 35. Joints involved: Both terminal thumb joints, proximal interphalangeals of both index fingers and of 5th right finger, both wrists, knees, shoulders, hips, temporomandibulars and right carpus and ankle	51%	51%	9%

A summation of the total percentage of total possible inflammation and deformity to be found in a given case can be readily made by referring to Table 4 in which the relative values for each joint have been calculated for each of four grades which may be designated as Minimal, Slight, Moderate and Maximal, or, as 25%, 50%, 75% and 100%.

In the case of grading inflammation, no rigid criteria for each grade can be laid down. Most clinicians will probably

agree fairly consistently concerning both minimal and maximal categories, but there will be a large element of subjectivity in defining what is "moderate" or "slight." Furthermore, we cannot pretend that a "grade IV" inflammation is exactly, or even approximately four times as great as a grade I, or twice that of a grade II inflammation. These difficulties, however, are inherent in any scheme for grading joint findings and do not stem from our proposed method for summing up these findings.

In the case of grading restriction of joint motion the situation is different, since this can be done with great accuracy with the aid of a goniometer, and with acceptable accuracy by mere clinical estimation. For summing up degrees of restricted motion it is theoretically possible to calculate the exact percentage of loss of full motion for each joint and to express this in terms of joint size, but the extensive calculations required are too cumbersome for practical use. We, therefore, suggest simple grading into 4 (or more) categories as outlined in Table 4, remembering that a summation of restricted joint motions will not necessarily tally with the degree of functional impairment, since the usefulness of joints does not depend entirely on their size.

In conclusion, we reiterate that our data as to joint size have their main clinical application in estimating the "spread" of rheumatoid arthritis. We are at present exploring the value of summations of deformity in relation to degrees of functional impairment, arrived at by other methods. We feel less certain of the value of summations

TABLE 4.—FOR SUMMING UP GRADES OF TOTAL POSSIBLE JOINT INFLAMMATION AND DEFORMITY

	Grade I Minimal (0–25%)	*Grade II Slight* (26–50%)	*Grade III Moderate* (51–75%)	*Grade IV Maximum* (76–100%)
Each terminal interphalangeal	0.2	0.5	0.7	1
Each proximal interphalangeal	0.5	1	1.5	2
Each metacarpophalangeal	1.3	2.5	3.8	5
Each carpometacarpal	1	2	3	4
Transverse intercarpal joints	3.7	7.5	11.2	15
Wrists	3.7	7.5	11.2	15
Elbow	13	26	39	52
Shoulder	11	22	33	45
Acromioclavicular	1	2	3	4
Sternoclavicular	3	6	9	12
Temporomandibular	1	2	3	4
Terminal interphalangeals (toes)	0.1	0.2	0.3	0.5
First proximal interphalangeal	0.7	1.5	2.2	3
Each remaining proximal interphalangeal	0.2	0.5	0.7	1
First metatarsophalangeal	2	4	6	8
Each remaining metatarsophalangeal	1.3	2.5	3.8	5
Transverse intertarsal area	3	6	9	12
Tarsometatarsals (together)	6	12	18	25
Talonavicular-calcaneocuboid	5	10	15	21
Talocalcaneal (subastragalar)	4.5	9	13.5	18
Ankle	8.7	17	25.7	35
Knee (including patella)	26	52	78	104
Hip	20	41	62	82

To determine the per cent of total possible inflammation or deformity, write down the values for each involved joint according to grade. Add these up and place a decimal point before the last digit. (The Table is arranged so that grade IV [or 100%] equals the figure 1 and the lesser grades are expressed as fractions thereof.)

of degrees of joint inflammation, partly because of the large subjective element which is involved in such grading, and partly because preliminary explorations suggest that the systemic indices of activity are a more sensitive indicator of what is going on, and have the great advantage of relative speed and simplicity.

Summary. The authors present anatomical measurements of the area of bone ends which together form the peripheral joints. The total peripheral joint surface so obtained is almost exactly one square meter. Using these areas as an index of relative joint size, it is possible, by referring to Table 2, rapidly to calculate the percentage of total possible joint involvement in a given case of rheumatoid arthritis. This is referred to as the "spread" of the disease.

By referring to Table 4, in which degrees of total possible inflammation and deformity are expressed in four grades, it is also possible to calculate in a given case of rheumatoid arthritis the percentage of joint inflammation and joint deformity.

The main clinical application of these measurements of joint size will be in determining the "spread" of the disease. The activity of the disease is more quickly and easily determined by a summation of the systemic manifestations of rheumatoid activity (to be presented in a subsequent paper). The value of summations of deformity in relation to degrees of functional impairment is being explored.

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SUMMARIO IN INTERLINGUA

Quantitation del Manifestationes de Arthritis Rheumatoide 4. Area Total del Articulationes Involvite Como Indice del Total Inflammation e Deformitate

Le autores presenta mesurationes anatomic del area de extremitates ossee que constitute, in lor summa, le articulationes peripheric. Le total area de superficie del articulationes peripheric es, secundo iste determination, quasi exactemente un metro quadrate. Si on usa iste areas como indice del relative dimensiones del articulationes, on pote, per referer se a tabula 2, calcular rapidemente le procentage del involvimento articulational in un date caso de arthritis rheumatoide in relation al possibile involvimento total. Iste procentage es designate como le "extension" del morbo.

Per referer se a tabula 4, in que grados del total possibile inflammation e deformitate es differentiate pro casos "minimal," "leve," "moderate," e "maximal," on etiam pote calcular le procentage de inflammation e de deformitate articulational presente in un date patiente de arthritis rheumatoide.

Le principal application clinic de iste mesurationes del superficies articulational va esser lor uso in determinar le "extension" del morbo. Le activitate del morbo es plus rapide- e facilemente determinabile per un summation del manifestationes systemic del activitate rheumatoide. (Isto va esser tractate in un articulo futur.) Le valor de summationes de deformitate in relation al grado de dysfunction es currentemente sub investigation.

PRO-BANTHINE IN THE TREATMENT OF PEPTIC ULCER

A CLINICAL EVALUATION WITH GASTRIC SECRETORY, MOTILITY AND GASTROSCOPIC STUDIES. REPORT OF 60 CASES*

By Jacob Lichstein, M.D.
ASSISTANT CLINICAL PROFESSOR OF MEDICINE

WITH THE CO-OPERATION OF

Margaret G. Morehouse, Ph.D.

AND

Kent L. Osmon, M.D.
FELLOW IN GASTROENTEROLOGY

(From the University of Southern California School of Medicine, Department of Medicine [Gastroenterology], Los Angeles County Hospital and the Cedars of Lebanon Hospital, Los Angeles, California)

The purpose of this paper is to report a study of the clinical effects of an anticholinergic drug, Pro-Banthine (SC–3171), B-diisopropylaminoethyl xanthene-9-carboxylate methobromide)*, on patients with peptic ulcer, with special attention to its ability to relieve pain and its influence on gastric secretion and motility.

Pro-Banthine was developed[5] in an attempt to find a drug similar to Banthine but of greater potency and free from the undesirable side effects not infrequently exhibited by the latter as a result of widespread parasympathetic inhibition. It was hoped thereby to achieve more closely the ideal of an antisecretory drug as expressed by Kirsner, "as a safely administered compound that consistently inhibits the output of hydrochloric acid for long periods after oral ingestion without development of tolerance and with minimal or no side effects"[7].

Sixty cases of ulcer were treated over a 24-month period with Pro-Banthine and investigated with reference to effectiveness and duration of pain relief and incidence of side effects. In addition we studied the effect of the orally-ingested drug on morning basal gastric secretion with respect to volume, pH, clinical units of acidity and milligrams of hydrochloric acid under varying stimuli of induction of secretion. In another phase of the study, tracings of gastrointestinal motility in response to the intramuscular and oral administration of Pro-Banthine were obtained by means of the multi-lumen tube, balloon kymograph method and the direct writer oscillograph recorder with amplification.

In another aspect of the project we concerned ourselves with a comparison of the usefulness of Pro-Banthine to that of Banthine employed previously in a group of the same patients during recurrent ulcer attacks. We were interested also in the clinical use of Pro-Banthine in an additional group of related gastrointestinal disorders in

*This study was made possible by a grant from, and liberal supplies of the drug were provided by, G. D. Searle & Co. (J. William Crosson, M.D., Assistant Director of Clinical Research).

which it seemed that the drug might have an indication by reason of its reported effect on secretion and gastrointestinal motility.

Our findings were documented by an intensive and personal observation of these patients over a 2-year period in private practice, and in two large hospital clinics with close supervision and satisfactory follow-up studies. It was found that the drug proved almost invariably effective in the relief of ulcer pain, in depressing gastric secretory volume and in inhibiting gastrointestinal motility. The incidence of side effects was minimal and significantly less than with Banthine. It was also useful in a smaller series of cases not included in the ulcer group in the acute diarrheas incident to the chronic functional gastrointestinal disturbances grouped under the term "irritable bowel."

A more detailed discussion of our experiences will permit of some qualifications of the generalizations stated in these prefatory remarks.

Method of Study. A. CLINICAL EVALUATION. All the patients in the ulcer series were proven by Roentgen-ray studies to show an active or chronic recurrent duodenal ulcer. A considerable number in the series were found to have been treated during previous attacks with Banthine, thus serving as their own controls and enabling us to compare the incidence of side effects of Pro-Banthine as against Banthine in the same patients.

The history in a considerable number in the group included some form of gastric operation for the existing ulcer state. Here we were afforded an opportunity of gauging the effectiveness of this anticholinergic drug in the obviously more difficult and long-standing problems.

The drug was never employed alone in treatment but was always prescribed together with a graduated ulcer diet and some form of antacid therapy. Mild sedation was supplemented when indicated. In the early months of the study the dosage in the average case was 30 mg. of Pro-Banthine t.i.d. and at bedtime, but we soon learned not to hesitate to increase the amount of drug until the desired relief was obtained. Flexibility of dosage was apparent early in the study and doses of 60 mg. or more four times a day were employed.

Patients were seen at weekly intervals. Relief of ulcer pain was judged on the basis of rapidity of action, effectiveness of relief, duration of relief and, where practical, an attempt at estimating healing time by periodic Roentgen-ray studies. We were especially interested in any spontaneous unsolicited comments on the presence of side effects. When patients did not volunteer comment on side effects, this fact was noted, following which they were specifically questioned on this point and the intensity of the side effect recorded. Side effects noted were dryness of mouth, blurring of vision, headache, difficulty in swallowing, urinary disturbance, constipation, heart palpitation, or bitter aftertaste (0 = none, +1 = slight, +2 = mild, +3 = moderate, +4 = severe).

In a small series, intervals of 6 months to a year occurred between the course of treatment and further follow-up and since we were interested in noting the possible effect of the drug on the prevention of recurrences, some attention was directed to this point in our study.

A small group of cases which included hypertrophic gastritis, peptic esophagitis, functional dyspepsia, irritable colon, regional ileitis, chronic ulcerative colitis and chronic recurrent pancreatitis were also included in the clinical phase of the study.

B. EFFECT ON GASTRIC SECRETION. The effect of single doses of Pro-Banthine on gastric secretion when administered intragastrically was studied by the method described by Kirsner and Palmer[6]. It has been shown that the parenteral administration of an anticholinergic drug affects the volume more constantly than the pH. We felt that the results of parenteral administration of the drug could not be applied clinically on a practical basis, and, therefore, we confined our gastric secretory studies to the intragastric administration of varying doses of Pro-Banthine. The series included normal individuals, patients with duodenal ulcer and others with related gastrointestinal conditions. The method consisted of the determination of the morning basal secretion in 21 cases. Following a 12-hour fast, a Rehfuss tube was introduced into the stomach and gastric aspirations were obtained every 15 minutes for 1 to 1½ hours. At this point doses of Pro-Banthine powder varying from 40 mg. to 80 mg. dissolved in small amounts of water

were administrated intragastrically. A waiting period of a half to one hour was then instituted to allow for drug absorption, following which specimens were obtained and the effect observed on the volume, pH (as determined by a Beckman pH meter), clinical units of free and total acidity by titration and milligrams of HCl at 15-minute intervals. The drug was administered in this manner either alone or with effective doses of histamine phosphate, a cholinergic drug such as urecholine, insulin, or a test meal in an attempt to evaluate the ability of oral Pro-Banthine to block the secretory response induced by these stimulants. Response was thus studied for periods from one hour to 145 minutes. The number of cases, dosages and stimulants employed are listed below.

TABLE 1.—TWENTY-ONE CASES OF DUODENAL ULCER, RELATED GASTROINTESTINAL DISORDERS, AND NORMALS IN WHOM GASTRIC SECRETORY STUDIES WERE PERFORMED WITH USE OF PRO-BANTHINE INTRAGASTRICALLY.

No. of Cases	*Dosage (mg.)*	*Stimulation Method*
5	40	None
1	60	None
3	80	None
3	40	Histamine
1	60	Histamine
2	80	Histamine
1	40	Urecholine
1	60	Urecholine
2	60	Insulin
2	80	Test meal

Total = 21

C. MOTILITY. A third phase of our study consisted of the evaluation of the intramuscular and oral effect of Pro-Banthine on gastrointestinal motility. Since the pain of ulcer is ascribed by one group of observers as being associated with increased gastric motility, studies of inhibition of motility seemed to us indicated. Motility records of the stomach, jejunum and sigmoid colon were obtained on 15 occasions in 8 cases by means of the traditional direct pressure recording obtained with a balloon and multilumen tube attached to a water manometer and recorded by an ink writer on a kymograph tracing. Simultaneous recordings were also made of the changes in gastric wall movements by means of a method whereby minute changes in intestinal wall pressures are obtained by the use of pressure transducers in the stomach and a strain gauge analyzer connected to a direct writer oscillograph recorder.

D. GASTROSCOPIC DATA. Thirteen cases in the ulcer series were gastroscoped periodically while under therapy and attention directed to the tone of the gastric wall, the color of the mucosa, the rapidity of peristaltic activity before and after the exhibition of the drug.

Results. A. CLINICAL EVALUATION. *1. Effect of Pain.* In 60 cases treated with the drug in the manner described, 46 were brought under control symptomatically within 24 to 72 hours. The pain relief was often immediate and its duration was maintained for from 3 weeks to 3 months. Of the 60 cases, 7 reported as not obtaining relief, one patient developed a severe intolerance to the drug and in four, the follow-up was unsatisfactory. Therefore, out of 56 cases of ulcer adequately studied, 48 obtained relief (89%). This compares with a report of Schwartz and his associates who found 106 cases of ulcer completely relieved of pain, twelve significantly relieved in a group of 129 cases[12]. The relief of pain was the most characteristic and outstanding response which occurred following the administration of the drug. In seven instances the improvement began after the first few doses, whereas the pain had been previously present, and was of relatively great intensity for a number of weeks. Individual case reports would seem to attest in a more dramatic manner the value of the drug in this regard as compared with a statistical recital.

In the 11% of failures, these patients showed on detailed study the presence of deeply ingrained anxiety manifestations of psychoneurotic proportions. The measure of the intolerance to the drug often served as an approximate yardstick of the degree of intensity of the psychosomatic component. This observation has been commented upon by others in connection with other pharmacologic studies on the intestine[13].

2. Comparison of Pro-Banthine and Banthine in 20 Ulcer Cases. An advantage gained by reason of the long-term features of this study was an opportunity to observe the clinical effects of Pro-Banthine and Banthine in the same ulcer patient during recurrent attacks. Twenty such cases were followed. In most instances where the pain relief was equally comparable in its immediacy, effectiveness and duration, we were impressed with the decreased side effects with Pro-Banthine. The patients in this group invariably expressed satisfaction with the newer anticholinergic. In 3 cases, however, Pro-Banthine did not prove as satisfactory. As one patient put it, in spite of the "cutting" effect and the presence of extreme mouth dryness of Banthine he preferred to revert to the former therapy to obtain the desired relief.

3. Incidence of Side Effects. In the 60 cases of ulcer where we tabulated the side effects, 42 (70%) had none of any kind, twelve or 20% had slight effects, while 6 cases (10%) had moderate to severe side effects requiring cessation of the drug. In the Banthine series of 20 cases drawn from the same group, 6 (22%) had no side effects, 4 had slight side effects (20%) and 11 (55%) had moderate to severe reactions making it necessary to discontinue the drug.

Therefore, 90% of the cases in the Pro-Banthine series had no, or slight, side effects, (obtained only on questioning) while in the Banthine series, 42% had no, or slight, side effects. These observations would seem to be of added significance in view of the fact that the same cases acted as their own controls during recurrent attacks.

The side effects with Pro-Banthine in our cases were almost exclusively confined to dryness of the throat. There was a lesser incidence of headache, "bitterness in the mouth," and constipation. In 2 cases, difficulty in urination was experienced and in one, increased frequency.

Three patients (of whom two were physicians) reported the onset of distinct but transitory muscular weakness of the upper and lower extremities which followed exhibition of increased doses of the drug. These symptoms did not prevent the patients from continuing the medication. It is of interest that observations in the experimental animal have shown that Pro-Banthine in very large doses has a curare-like effect on voluntary muscles as manifested by somatic neuromuscular blockade and respiratory depression. An intravenous dose of 6.4 mg. per 1 kg. produced complete sciatic nerve blockade lasting a few minutes in the experimental animal[5].

TABLE 2.—COMPARISON OF INCIDENCE OF SIDE EFFECTS OF PRO-BANTHINE AND BANTHINE

	No. of Cases	*None*		*Slight*		*Severe*	
		No.	*%*	*No.*	*%*	*No.*	*%*
Pro-Banthine	60	42	70	12	20	6	10
Banthine	20	6	22	4	20	11	55

Wide patient drug tolerance to the drug was demonstrated as evidenced by the ability of the patients to take the drug steadily for many months without any untoward effects and by the ability to tolerate sudden large increases.

4. Effect on Surgical Indications and Incidence of Recurrence. That the use of Pro-Banthine does not preclude the need for surgery is shown by the fact

that 5 of our patients eventually were subjected to operation (8%) after it was concluded that medical management was ineffective. Three underwent vagotomy and pyloroplasty, and two, subtotal gastrectomy. The percentage of patients reaching surgery in the general ulcer population varies, but it would seem that this figure does not indicate any decrease. In 3 patients during the course of therapy, recurrences took place. In 3 additional instances, operation was advised, but the patients demurred at the time the study was terminated.

Hemorrhage, either moderate or massive, occurred as a complication in 13 cases (21%) at one time or another. It can therefore be considered that the drug was given a rigorous trial. This is attested by the fact that in this group, ten had been severe enough prior to this study to warrant operation, 5 procedures being of an emergency nature.

5. The Place of Pro-Banthine in Related Gastrointestinal Disorders. The drug was employed in 16 cases of functional dyspepsia, chronic ulcerative colitis, peptic esophagitis, regional ileitis and chronic recurrent pancreatitis. The value of Banthine in the unstable bowel was recently studied by us by means of the double-blindfold placebo control method[9], and we were impressed by its short-term effectiveness in diminishing the diarrhea, but not in its over-all long-term usefulness. We were, therefore, interested in gathering data on the possible increased effectiveness of Pro-Banthine in this regard. In the "unstable colon" syndrome, it was invariably found useful in controlling the diarrhea which periodically occurs during acute exacerbations, probably by reason of its effect in inducing hypomotility.

Its value in the diarrhea of ulcerative colitis, regional ileitis and chronic recurrent pancreatitis was less well documented, but in specific cases when used for the recurrent diarrhea incident to these disorders, it was followed by a decrease in the number of bowel movements, and at times its exhibition during acute exacerbations appeared to be followed by subsidence of distress. This latter finding must be considered in the light of, 1) the known tendency of these conditions to undergo spontaneous remission, 2) the essentially tentative nature of the most astute clinical observations.

In 5 cases of combined duodenal ulcer and irritable colon, the drug seemed doubly indicated and was employed. We learned to avoid the hazard of inducing or aggravating an existing constipation in these patients and used sedation and belladonna alkaloids alternating with the anticholinergic.

6. Gastroscopic Observations. Gastroscopic examinations were performed 13 times in this series. Nine were normal and 4 gave evidence of a gastritis either of the superficial, atrophic or hypertrophic type. Where a gastritis was associated with an ulcer, it was our impression that clinical improvement was more difficult to maintain.

The effect of Pro-Banthine on the gastric mucosa was studied in three cases. It is to be noted that pallor, bogginess and lack of peristaltic activity has been reported gastroscopically following vagotomy[10]. A similar effect was most strikingly noted in our observations, to the extent that when roentgenograms were performed at the same time, retention of the barium was noted in appreciable amounts and was interpreted by the roentgenologist as "pylorospasm," whereas atony of the stomach proper, quite evident gastroscopically, was actually the most probable cause of the barium delay.

7. Effect on Gastric Secretion. On the basis of 22 gastric secretory studies, the intragastric administration of the

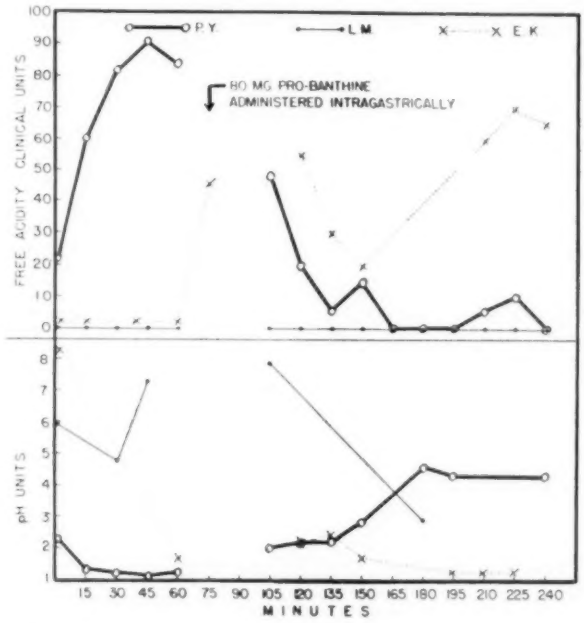

Fig. 1.—Effect of intragastric administration of Pro-Banthine upon the acidity of nonstimulated gastric secretion in 3 patients.

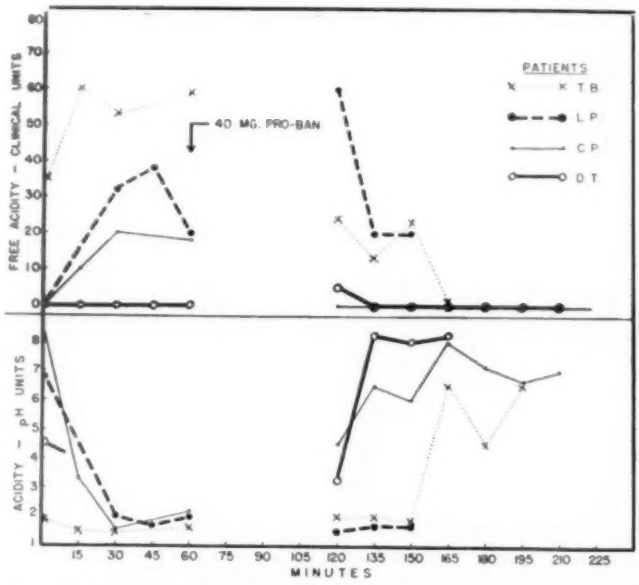

Fig. 2.—Effect of oral administration of Pro-Banthine upon acidity of nonstimulated gastric secretion.

drug in the higher dose range invariably produced a decrease in volume output of gastric secretion, whereas, while it did depress the clinical units of acidity or raise the pH in individual cases (Fig. 1), it did not do so as invariably as it affected the volume. These studies indicate also that the anti-secretory effect of Pro-Banthine is similar to that of Banthine without inducing the side effects.

B. EFFECT UPON STIMULATED SECRETION (12 CASES)

a. Histamine (6 Cases). When effective doses of histamine were challenged with 40- and 60-mg. doses of Pro-Banthine intragastrically, the effect was that of a volume reduction and in 2 cases, a decrease in free acidity followed this procedure (Figs. 4 and 5).

b. Insulin (2 Cases). When 60 mg. of Pro-Banthine were given at the time

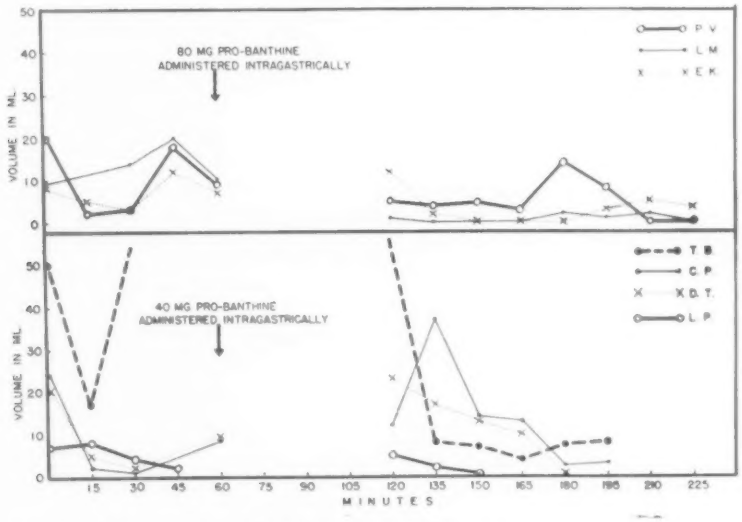

Fig. 3.—Effect of intragastric administration of Pro-Banthine upon volume of nonstimulated gastric secretion (comparison of dose levels).

A. EFFECT OF INTRAGASTRIC PRO-BANTHINE UPON NONSTIMULATED SECRETION (9 CASES). An 80-mg. dose appeared in general to reduce volume. The effect of a 40-mg. dose was questionable, although the trend was towards a reduction in volume. A diminution of free acidity with the 80-mg. dose occurred (Fig. 1); the 40-mg. dose was followed by a lessening of free acidity which appeared more striking possibly due to individual patient variation (Fig. 2).

The effects of oral administration on volume are shown in Fig. 3.

of achieving an effective drop in blood sugar level, no significant drop in volume, acidity, or rise in pH occurred in 2 cases of chronic recurrent duodenal ulcer (Fig. 6).

c. Urecholine (2 Cases). Where a 4-mg. dose of urecholine was used, Pro-Banthine, in doses of 40 and 60 mg. did not produce any striking change in volume and acidity (Figs. 7 and 8).

d. Test Meal. In 2 cases where a meal was given, there was a variability in response to volume, acidity, pH and mg. HCl with 80 mg. Pro-Banthine (Tables 3 and 4).

TABLE 3.—EXAMPLES OF DATA OBTAINED FROM GASTRIC SECRETORY STUDIES IN CASE 1 WHERE THE DRUG WAS ADMINISTERED WITH A TEST MEAL. NOTE VARIABILITY IN RESPONSE OF VOLUME, ACIDITY AND MG. HCl.

Patient: W. S.
Diagnosis: Chronic Recurrent Duodenal Ulcer

Date: July 21, 1953
P.F. No. 194–339
Tube administered: 9:00 A.M.
Tube withdrawn: 12:50 P.M.

CONTROL

Interval	*Sample No.*	*Vol.*	*pH*	*Acidity* Free	*Acidity* Total	*Mg. HCl* Calc. from Titr.
0	Residual	3.0	..	21.3	44.0	77.6
15	1	3.5	..	25.7	56.5	93.8
30	2	9.0	..	17.9	31.0	65.3
45	3	6.0	..	25.6	37.0	93.0
60	4	8.0	..	24.0	37.6	88.0

10:00 A.M.: 80 mg. Pro-Banthine administered.
Breakfast given: 1½ boiled eggs, 1 piece zwieback buttered, 1 cup milk. Complained later of pain and burning sensation, dry mouth.

30	Control	5.0	..	0.0	12.0	0.0
15	1*	10.0	..	0.0	16.8	0.0
30	2*	17.0	..	0.0	34.0	0.0
45	3*	1.0	..	0.0	11.2	0.0
60	4*	3.0	..	0.0	34.6	0.0
75	5*	43.0	..	0.0	58.1	0.0
90	6†	7.0	..	0.0	72.0	0.0
105	7†	3.0	..	0.0	67.7	0.0
120	8†	0.6	..	0.0	44.0	0.0

* Food partially digested, pieces of egg and bread, finer particles seen as digestion proceeds.
† Much less food, digested blood.

TABLE 4.—EXAMPLES OF DATA OBTAINED FROM GASTRIC SECRETORY STUDIES IN CASE 2 WHERE THE DRUG WAS ADMINISTERED WITH A TEST MEAL. NOTE VARIABILITY IN RESPONSE OF VOLUME, ACIDITY AND MG. HCl.

Patient: S. R.
Diagnosis: Duodenal Ulcer

Date: August 4, 1953
P.F. No.: 1245–067
Tube administered: 9:00 A.M.
Tube withdrawn: 12:45 P.M.

CONTROL PERIOD

Interval	*Sample No.*	*Vol.*	*pH*	*Acidity* Free	*Acidity* Total	*Mg. HCl* pH Calc.	*Mg. HCl* Titr. Calc.
0	Residual	4.0	..	0.0	3.4	..	0.0
15	1	15.0	1.98	12.0	24.8	38.2	43.9
30	2	3.5	1.54	29.0	40.8	105.3	106.0
45	3	1.0	..	20.4	32.6	..	74.5
60	4	..	..	..	..	..	..

10:02 A.M.: 80 mg. Pro-Banthine administered.
10:05 A.M. Breakfast: 1 piece buttered zwieback, boiled egg, 1 cup milk finished at 9:20 A.M. Later complained of pain

45	Control	24.0	5.48	0.0	28.0	..	
15	1	82.0	3.29	0.0	56.6	1.8	0.0
30	2	15.0	3.05	10.0	55.6	..	36.5
45	3	60.0	1.62	26.6	68.6	87.6	97.2
60	4	36.0	1.70	30.6	70.6	72.8	111.3
75	5	7.0	1.62	40.0	74.6	87.6	145.0
90	6	8.0	1.73	42.0	65.6	68.0	154.0
105	7	4.0	..	30.0	46.0	..	109.8
120	8	3.0	..	14.0	36.0	..	51.1

Remarks: Food particles were present in all samples after breakfast, filtrates were cloudy, and may have interfered with electrodes or pH meter may not have been accurate as some drift was apparent. Would feel titration values most accurate.

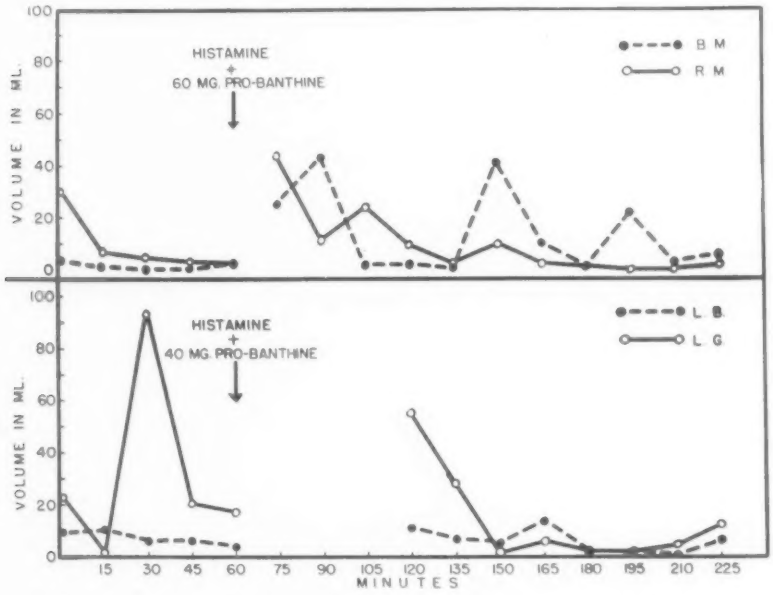

Fig. 4.—Effect of administration of Pro-Banthine upon histamine stimulated gastric secretion.

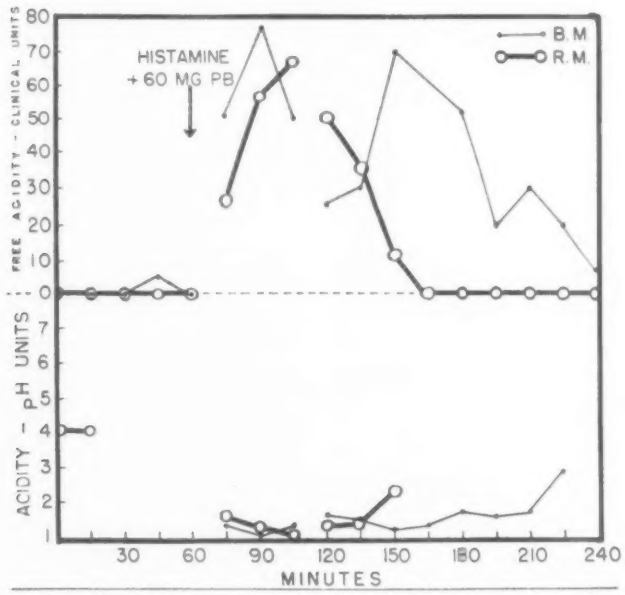

Fig. 5.—Effect of administration of Pro-Banthine upon histamine stimulated gastric secretion.

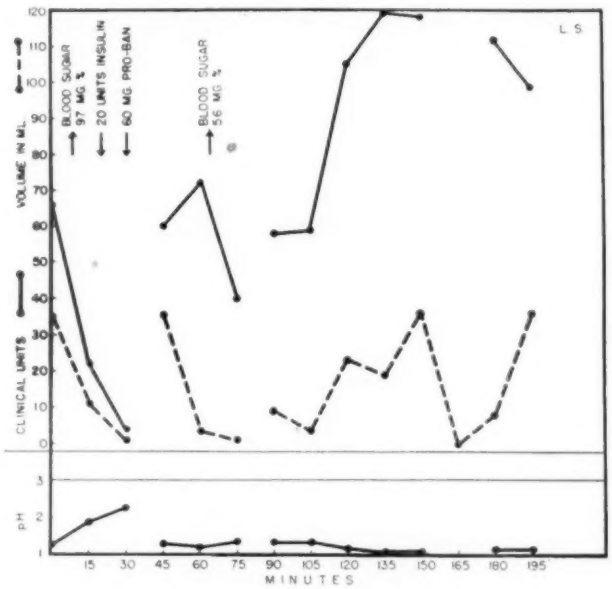

Fig. 6.—Effect of intragastric Pro-Banthine on insulin-induced gastric secretion.

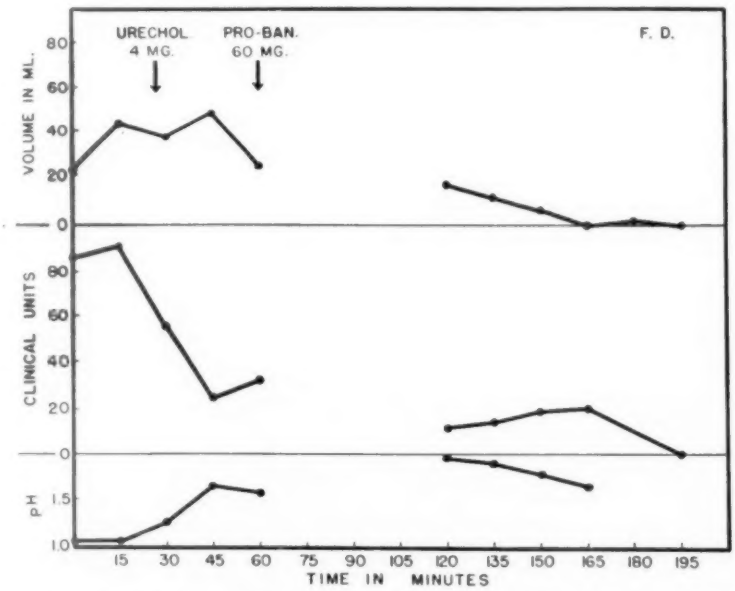

Fig. 7.—Effect of oral administration of Pro-Banthine upon gastric secretion after urecholine stimulation.

8. *Effect on Gastric Motility.* The intramuscular injection of Pro-Banthine produced a decrease in gastric motility when studied in normal individuals, in patients with duodenal ulcer, and in related gastrointestinal disorders. The accompanying tracings (Figs. 9 and 10) illustrate this inhibitory effect when measured by means of the balloon-water manometer kymograph method and a method whereby minute pressure changes in the gastric wall were picked up by strain gauges and amplified by an analyzer and recorded by a direct writing oscillograph. It will be noted that the effect was produced in minutes; this was maintained from one-half to two hours. This new method has been hitherto undescribed[8].

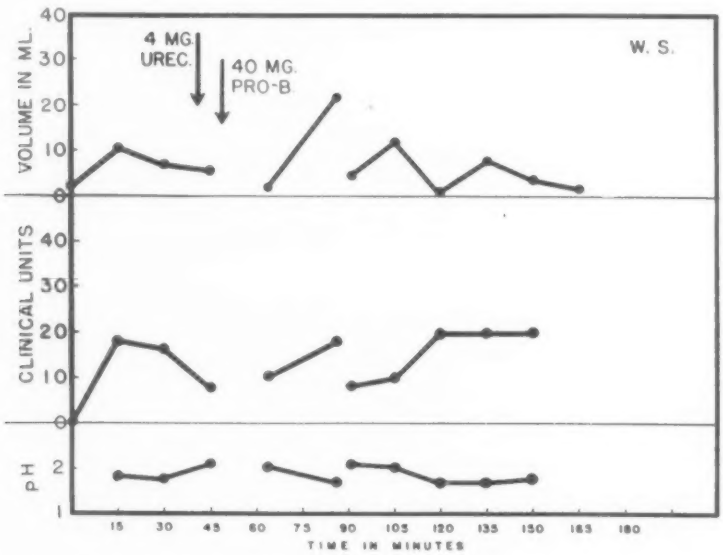

Fig. 8.—Effect of oral administration of Pro-Banthine upon gastric secretion after urecholine stimulation.

Case Reports. CASE 1. R.H., a white male, aged 64, (Los Angeles County Hospital, P.F. #1361–866) was first seen May, 1953. His clinical history included intermittent attacks of epigastric pain since 1938. Three years ago his pain had become more constant and was associated with severe night pain lasting from 11:30 p.m. to 3:00 a.m. daily, relieved only by milk and antacids. A duodenal ulcer had been established by roentgenological criteria on May 15, 1953. He was placed on Pro-Banthine, 30 mg. every 6 hours, a half ounce of Creamalin every 4 hours and an "ambulatory" ulcer diet. On the third day he experienced clear-cut relief of pain and the night pain disappeared. When next seen on May 29, 1953, he continued to be asymptomatic. Relief continued and was maintained through June until July 10. In this period, when questioned as to side effects, he stated that he had some dryness of the throat. On July 10, he had a recurrence of night distress and epigastric discomfort during the day. The dosage was thereupon increased to 60 mg. of Pro-Banthine q.i.d. and he again was free of symptoms for the following 3 months. In August, he reported a weight gain of 6 pounds in 6 weeks, with occasional night pain when he lapsed from treatment. In November, he fell into the habit of taking Pro-Banthine and an antacid at 9:30 p.m. before going to bed. When last seen on May 28, 1954, one year later, he had remained comfortable under this regimen.

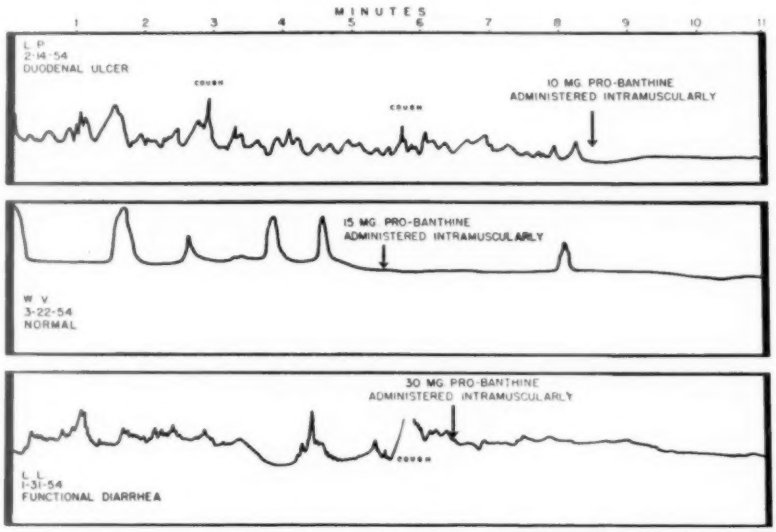

Fig. 9.—Effect of intramuscular Pro-Banthine on gastric motility (Balloon-Water Manometer Kymograph Method).

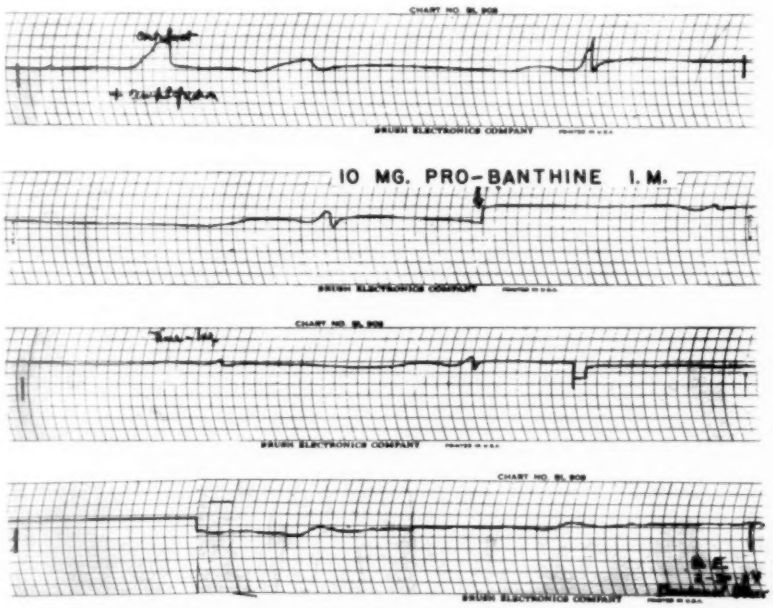

Fig. 10.—Depression of gastric motility following Pro-Banthine i.m. as obtained by a new direct method of recording gastrointestinal pressures[8] with transducer and amplification.

Laboratory Data: November 24, 1953: Roentgenographic study indicated a chronic duodenal ulcer. April 22, 1954: Films showed a persistently deformed duodenal cap. Diagnosis: Duodenal ulcer. No change is seen in these films when compared with those of November 24, 1953.

This case exemplifies the promptness and long duration of pain relief which occurred with the use of Pro-Banthine on a long-term basis in a case of long standing severe duodenal ulcer in the face of no change roentgenologically.

CASE 2. C.R., a white female, aged 29 (private case) was first seen April 20, 1954, with an intermittent chronic diarrhea of 2 years' duration. Gastrointestinal roentgenograms, repeated stool examinations, and two sigmoidoscopies were negative except for the presence of a benign gastric prolapse into the duodenum. A diagnosis of psychogenic diarrhea was entertained clinically. She was placed on Pro-Banthine, 30 mg. t.i.d. a.c. on May 1, and in 48 hours her diarrhea ceased and was followed by a pronounced constipation, so that the dosage of the drug was reduced, and later replaced by a combined antispasmodic and sedative. She was asymptomatic until July 21, when diarrhea recurred and was again controlled by 2 days of Pro-Banthine by mouth. Two less severe attacks responded to a similar regimen up to the time of this writing.

This case illustrates the short-term effectiveness of Pro-Banthine in this particular patient and is typical of our experience with other cases of so-called acute "emotogenic" diarrhea incident to the "unstable colon."

CASE 3. F.L.D., a colored male, 35 years of age, was first seen August 7, 1953. His ulcer symptoms dated since the age of 20. He was discharged from the Army in 1941 on this basis. A roentgenographic study on July 18, 1951, disclosed an irregular duodenal bulb with point tenderness over the duodenum. Despite strict adherence to ulcer management, with alkalis and antispasmodics, he had constantly recurring attacks of pain, vomiting and hematemesis each spring. There was persistent epigastric pain, gnawing in character and radiating to the right. A recent trial with Banthine as an adjunct was followed by gastric irritation and pain. He was hospitalized for an attack of pyloric obstruction one year prior to August of 1954.

When first interviewed, he was fairly comfortable except for "gas" in his right side and the "shakes" in the morning and evening. He was placed on Pro-Banthine 30 mg. t.i.d. and h.s. and developed nausea, and vomiting for 2 days. These symptoms continued when the dosage was decreased. He stated that he could tolerate Banthine but not Pro-Banthine. In the latter part of October he reported that the Pro-Banthine helped him by stopping "his misery" but that it was followed invariably by nausea and vomiting. On November 30, 1953, since he could no longer work because of the pain, a pyloroplasty and vagotomy were performed (Drs. C. J. Berne and William Snyder) and a large ulcer on the posterior wall penetrating into the pancreas was found at operation.

Discussion. The etiology of peptic ulcer remains obscure, but the desideratum in the control of the problem of ulcer would appear to be the continuous and sustained inhibition of gastric acidity and the assured prevention of recurrences of ulcer distress. Our theories with regard to the neural and hormonal mechanisms involved in acid production may be in the process of becoming translated into specific physiologic mechanisms.

For the present, we must content ourselves with the more limited means immediately available to us. The anticholinergic group of drugs, effective at the post-ganglionic level, offer themselves as potent tools to the clinician in the control of ulcer pain and inhibition of the volume of gastric secretion. Our experience in this study justifies the conviction that a drug such as Pro-Banthine can be employed for the relief of pain of ulcer. The maneuverability of dosage is an advantage hitherto not vouchsafed us.

A number of points concerning anticholinergic drugs bear discussion. What convincing data are available to show the clinical superiority of anticholinergic drugs over standard therapy? How dependable are the criteria for

the clinical evaluation of anticholinergic drugs in general? Is the anticholinergic effect powerful enough to withstand overwhelming stimulation from higher levels?

Two recent reports on the long-term effect of Banthine may cast some light on the first question. In 34 patients at the Aartius County Hospital, Copenhagen[3], one-third were free of pain after one year of Banthine, and one-fifth showed radiological healing of ulcer; it was felt that Banthine should be looked upon as no more than a useful supplement to the standard medical treatment of "gastric" ulcer and should not be given for more than 3 months at a time.

In another series[2], from the same hospital, 68 ulcer cases were given 50 mg. of Banthine three times daily and 66 were used as controls and treated with inert placebos. All were treated for 10 days in the hospital and were examined 2 and 10 weeks later. Sixty-five per cent of the Banthine-treated patients improved clinically and 23% showed radiological improvement. In the placebo group, 56% were improved and 14% showed improvement by Roentgenray. The conclusion was that Banthine was excellent for pain relief but not sufficient as an all-around remedy.

Ruffin[11], employing a "double blind study" in a study of 555 cases of ulcers with a 10 months' average follow-up, compared two anticholinergic drugs against atropine and a placebo. The placebo achieved good to excellent results in 48%, fair to poor in 52%; atropine achieved good to excellent results in 53%, fair to poor in 47%; each anticholinergic drug achieved good to excellent results in 74 to 75% and 25 to 26% fair to poor.

Stewart Wolf[4] and his co-workers tested the inhibitory effect of three quarternary amines against the stimulus of intravenously administered insulin or a stressful interview. Both stimuli broke through the inhibitory effects of all of the agents used.

The history of the attitude toward the place of anticholinergic drugs in gastroenterologic practice can be divided into three phases: 1) an initial period of great enthusiasm in which hopes were expressed that even the need for surgery might be lessened, and that a significant decrease in recurrences was to be envisioned, 2) a rebound period of excessive skepticism when a considerable number of therapeutic failures were encountered and side effects delimited the use of the drug, 3) and finally a realistic assessment of their proper role in treatment. This study, because of its long-term features, and detailed follow-up studies may afford data for a valid appraisal of the place of Pro-Banthine in the attack on the ulcer problem.

Conclusions. 1. Pro-Banthine is a valuable adjunct in the relief of pain of uncomplicated duodenal ulcer when used in conjunction with diet and antacids in medical management.

2. In 60 cases of peptic ulcer treated in this manner, 89% had immediate response with respect to promptness of relief of pain and duration of effective relief. Drug tolerance was good. This response was more noticeable in cases with first attacks.

3. Pro-Banthine was significantly less likely to produce side effects than Banthine when exhibited in the same ulcer case. In this series, 9 out of 10 had no side effects with the former drug while more than one out of two cases had severe side effects with the latter medication.

4. In the same series, Pro-Banthine proved equally as effective as Banthine in the relief of pain and the dosage schedules were more flexible.

5. The effect of Pro-Banthine on gastric secretory activity was such as in-

variably to depress volume of secretion; the degree of acidity as measured by pH, clinical units and mg. of hydrochloric acid was sporadically and not consistently affected.

6. Intramuscular injection of the drug consistently inhibited gastric motility as measured by the balloon and strain gauge oscillograph method. Intragastric administration was followed by a similar but slower and less dramatic effect on motility.

7. Gastroscopic observations in 13 cases in this study indicated an effect on gastric tone in 3 cases similar to that observed following vagotomy.

8. We were not impressed with any reduction in recurrence rate or decrease in incidence of complications or the lessened need for surgery in our cases when observed on a long-term basis.

9. In 16 cases of related gastrointestinal conditions, the parasympathetic inhibitory effect of Pro-Banthine on motility appeared to be clinically manifest only in the acute phases of the disorders. This was most strikingly seen in the acute diarrheas incident to functional gastrointestinal distress.

10. The final answer to the definitive control of the ulcer problem still waits upon further developments on an experimental basis in the physiological laboratory of the disturbed neurohumoral processes involved.

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SUMMARIO IN INTERLINGUA

Pro-Banthina in le Tractamento de Ulcere Peptic

1. Pro-Banthina es un adjuncto de valor in le alleviation de dolores in casos de non-complicate ulceres duodenal, si illo es usate in conjunction con mesuras dietari e con antacidos in le regime medical.

2. In 60 casos de ulceres peptic que esseva tractate in iste maniera, 89 pro cento monstrava un responsa immediate quanto al promptitude del alleviation de dolores e al duration efficace de ille alleviation. Le toleration del droga esseva bon. Iste responsa esseva plus notabile in casos de prime attaccos.

3. Le administration comparative de Pro-Banthina e Banthina in le mesme casos de ulcere supportava le conclusion que le probabilitate de effectos lateral es significativemente inferior in Pro-Banthina. In le serie hic reportate, 9 inter 10 patientes habeva nulle effectos lateral post Pro-Banthina, durante que Banthina produceva sever effectos lateral in un ex omne duo patientes.

4. In le mesme serie, Pro-Banthina se monstrava tanto efficace como Banthina in le alleviation de dolores, e le dosage de Pro-Banthina esseva plus flexibile.

5: Le effecto de Pro-Banthina super le activitate del secretion gastric se manifestava in un reduction invariabile del volumine secretori. Le grado de aciditate, mesurate in pH, unitates clinic, e mg de acido hydrochloric, esseva afficite sporadica- e non-uniformemente.

6. Le injection intramuscular del droga resultava uniformemente in un inhibition del motilitate gastric, mesurate per un methodo manometric a ballon e aqua con registration kymographic e peer un nove methodo (non ancora reportate in le litteratura) in que minime alterationes de pression in le pariete gastric es amplificate per un analysator e registrate per un oscillographo a inscription directe. Le administration intragastric del droga esseva sequite per un simile, ben que plus lente e minus frappante effecto super le motilitate gastric.

7. Observationes gastroscopic executate in 13 del casos includite in le presente studio indicava in 3 casos un effecto super le tono gastric que esseva simile al effectos observate post vagotomia.

8. Le observation a longe duration non resultava in le casos hic reportate in le impression que il habeva un reducite frequentia de recurrentias o un reducite frequentia de complicationes o un minus frequente necessitate de applicar methodos chirurgic.

9. In 16 casos de relationate conditiones gastrointestinal, le parasympathic effecto inhibitori de Pro-Banthina super le motilitate gastric esseva clinicamente manifeste solmente durante le phase acute del disordine. Iste observation esseva specialmente frappante in relation al diarrheas acute que occurre in connexion con functional disturbationes gastrointestinal.

10. Le solution final del problema de obtener un controlo definitive de ulceres depende ancora de disveloppamentos futur in le experimentation physiologic relative al disturbate processos neurohumoral involvite.

SUMMARIO IN INTERLINGUA

(See page 172 for original article)

Djenkolismo o Invenenamento per Semines de Djenkol (Pithecolobium Lobatum): Un Causa de Hematuria e Anuria

In certe personas le ingestion de semines de djenkol (Pithecolobium lobatum) causa a vices leve o sever grados de dysuria, colica, dolores lumbar e vesical, hematuria, e, minus frequentemente, anuria, hypertension e azotemia. Le causa es probabilemente a trovar in le effectos de acido djenkolic, sed le mechanismo de su action o le mechanismo del action de un non-cognoscite composito super le vias urinari remane a discoperir. Studios additional va possibilemente illuminar le mechanismo causative del hematuria e anuria.

DJENKOL BEAN POISONING (DJENKOLISM): A CAUSE OF HEMATURIA AND ANURIA

By Hobart A. Reimann, M.D.*

and

R. Utojo Sukaton, M.D.

(From The Djakarta Central Hospital, University of California—University of Indonesia Project in Medical Education, Djakarta, Indonesia)

Djenkol (jenkol, genkol) beans (*Pithecolobium lobatum*, family Mimosaceae) are relished as a food in Java and Sumatra. They grow in large pods on trees and are on sale in the markets most of the year. The ripe beans resemble somewhat flattened, large horse-chestnuts and when crushed emit a disagreeable, faint, sulfurous odor. They are eaten raw, fried or roasted. Occasionally they are buried and allowed to sprout beforehand. Regardless of the method of preparation, the ingestion of even one bean imparts a sulfurous fetor to breath and urine. Most persons eat the beans with impunity, but at times severe sickness follows. Persons who previously had eaten them without ill effect may be severely affected after one meal, but later may eat them without untoward manifestations. Poisoning may be caused by only one bean. The hazard is well-known but generally disregarded.

Mild djenkolism is characterized by spasmodic pain in the loin and bladder and by urine containing albumin, leukocytes, epithelial cells, casts, erythrocytes and needle-shaped crystals. Severe attacks are alarming. Within 2 to 12 hours after eating the beans there are intense colic, flatulence, meteorism, and painful micturition. Vomiting, diarrhea or constipation occur. The urine at first is "milky," but soon becomes bloody and reduced in amount. Transient anuria, hypertension and azotemia may follow. There may be low fever and leukocytosis. The majority of otherwise healthy victims recover within a few days. Death is rare. The history of eating djenkol beans, the characteristic odor of the breath and urine and crystalluria make diagnosis easy.

Sixteen adult patients entered the medical wards of the Djakarta Central Hospital in the past year, 10 of them in September and October. Their recorded histories were not always reliable or complete and facilities for detailed study were limited. They had eaten from 1 to 20 beans. Two had eaten them for the first time, ten had had them several times before without becoming sick and others did not remember. The symptoms began 2 to 12 hours later with dysuria and pain in the lower abdomen and lumbar areas. In 3 severe cases the blood pressure was over 150 mm. of mercury, but returned to normal after recovery. Gross hematuria was recorded in 10, oliguria in 10 and anuria in 4. Needle-like crystals were seen in the urine of 6. During the acute phase, the amount of urea in the blood varied from 20 to 70 mg. per 100 ml. in different patients. Treatment consisted of

*Present address: Binghamton City Hospital, Binghamton, New York.

the administration of 2 to 4 gm. of sodium bicarbonate several times a day and of water by mouth or parenterally if vomiting caused dehydration. Morphine occasionally was necessary to relieve severe pain. All were well by the third day. The following is a typical instance.

Case Report. A man, aged 38, stated that he ate three fried beans at noon. At 11 P.M. he was surprised when he voided urine that was at first milky, later bloody. Within an hour colic and lumbar pain became severe and persistent. He had eaten djenkol beans in the past without ill effect. His family partook of the same batch of beans which at this time affected him alone.

He came to the hospital in the morning. His breath was offensive and micturition was painful. Sweating was profuse but there was no fever or headache. He clasped his abdomen and writhed with colic. Pain was relieved by morphine. After brief vomiting and diarrhea, there was no bowel movement for 2 days. Except for abdominal and lumbar tenderness, there were no abnormalities on physical examination. The blood pressure was normal. The urine was bloody but normal in amount. Its reaction was acid and the specific gravity varied from 1.010 to 1.015. It contained blood, epithelial cells, and a few bundles and rosettes of needle-shaped crystals which rapidly disappeared. A few casts were seen. There was no anemia and the leukocytes numbered 7000. The blood urea measured 60 and 40 mg. per 100 ml. The symptoms disappeared on the second day but microhematuria persisted for 6 days.

Comment. Except for halitosis and malodorous urine such as occurs after eating asparagus, djenkol beans apparently are harmless to most persons. It is unknown why, at times, a few are poisoned. Perhaps there occur varying degrees of unrecognized disturbance with microhematuria, mild dysuria and mild abdominal pain. Only those who are severely sick seek medical aid or enter a hospital. The suggestion has been made that djenkol beans vary in toxicity depending on their source and age or on the mode of preparation for food. It is more likely that changes in susceptibility or hypersensitivity of the victim to a noxious agent is responsible for djenkolism. An hereditary predisposing factor may exist as it appears to in favism from the fava bean *(Vicia fava),* another legume[2].

There has been surprisingly little investigation of this unique disease. While it is of practical importance chiefly to local physicians who deal with it, it is of academic interest because the beans contain a substance which may cause hematuria, anuria, hypertension and azotemia. Isolation of the active principle may furnish a useful tool for the study of these important clinical conditions, the underlying mechanisms of which are not well understood.

Several nephrotoxic antibiotics and other toxic or sensitizing drugs which injure the nephrons cause acute renal failure, but seldom with gross hematuria. Hemoglobinuria and hematuria occur in favism, but there rarely is anuria or renal failure. Cortical necrosis was observed in an infant[2]. Cantharidin a known vesicant, causes microhematuria by its irritant action. The cause of hematuria in djenkolism is unknown. It is believed by some (Van Veen and Hymans[5]) that the sharp crystals of djenkolic acid lacerate renal tissue and cause bleeding or cause obstruction as in the case of sulfonamide precipitation. This may be so, but reports of biopsies make no mention of crystals in the kidney and few appear in the urine. However, crystals may have been destroyed in the preparation of specimens for study. The turbidity of the urine early in the disturbance may be due to crystals or to desquamated cells. Blockage of the urinary tract may be caused by erythrocytes, yet no blood-casts, hemoglobin or clots appear in the urine. The few histologic studies of renal tissue reported fail to show obstruction by erythrocytes.

Of the causes of anuria listed by Wakim[6], obstruction of the urinary passages by compression from severe interstitial edema or by debris from necrosis and desquamation may occur in djenkolism, although proof is lacking. The kidneys may be edematous owing to an allergic reaction or other irritating effect on the renal parenchyma, on the capillaries, on the cells lining the urinary tract or even on the renal nervous system. Unfortunately no cystoscopic studies or urograms have been made to detect possible superficial changes in the urethra and bladder, or disturbances in the ureters and renal pelvis. Serial needle biopsies of the kidney might be informative. Dysfunction of the urinary tract dominates the clinical picture of djenkolism, but gastrointestinal symptoms suggest a direct or reflexive effect on that tract as well.

Only a few inconclusive studies on animals have come to our attention. Van Veen and Hymans[5] fed the beans to monkeys, but aside from crystalluria no changes were observed. Mreyen[4] fed beans to one monkey and to a few rabbits and guinea pigs. None became sick. Apparently no deliberate attempts at sensitization were made. Tissues of animals killed 6 to 24 hours after feeding are meagerly described. The lungs, kidneys, jejunum and liver were hyperemic. Occasionally there was a leukocytic infiltration of the peripelvic renal connective tissue and exfoliation and obliteration of some tubules. Biopsy made during renal decapsulation on two anuric patients showed swelling and exfoliation of the tubular epithelium in one. In the other there were a few leukocytes in the glomeruli and acute hemorrhagic inflammation in the perirenal tissue.

According to Van Veen and Hymans, the crystals in the urine are amphoretic and slightly soluble in water, but easily so in alkaline or acid solution. Chemically they resemble those of cystine; morphologically, those of tyrosine. Analysis of the beans revealed a substance precipitated by phosphotungstic acid after hydrolysis which they called djenkolic acid. It is an amino acid rich in sulfur with a suggested formula of $C_{11}H_{23}N_3S_3O_6$. Presumably it is the cause of djenkolism. When injected intraperitoneally into monkeys, it was excreted as such in the urine. Phenylacetic acid is a further split product. du Vigneaud synthesized *l*-cysteine thioacetal of formaldehyde which has the properties of djenkolic acid (Armstrong and du Vigneaud[1] and du Vigneaud and Patterson[3]).

Summary. Djenkol beans when eaten by some persons at times cause mild to severe degrees of dysuria, colic, lumbar and bladder pain, hematuria, and occasionally anuria, hypertension and azotemia. Djenkolic acid presumably is the cause but the mechanism of its action, or the action of some unknown compound, on the urinary tract remains to be discovered. Further study of the problem may throw light on the mechanism of the cause of hematuria and anuria.

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(Interlingua on page 171)

THERAPEUTIC AND TOXIC EFFECTS OF ENTERIC-COATED AMINOMETRAMIDE

By Walter A. Tatge, M.D.*

Donald E. Winnik, M.D.

and

George N. Spencer, M.D.

(From the Medical Service, Wood Veterans Administration Hospital, and the Department of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin)

Aminometramide, commercially available as Mictine, is an oral diuretic of rather recent development. It is a result of studies of xanthines and xanthine derivatives in an effort to isolate a more potent diuretic. It is a member of a group of 6-aminouracils found to produce a maximum of diuresis with a minimum of gastrointestinal irritation[4,5]. The pharmacologic action of this substance appears to reduce an elevation of the serum sodium and potassium, but does not seem to alter normal electrolyte values[2]. Kattus *et al.* indicated that it acts by inhibiting the reabsorption of sodium and chloride in the renal tubule[3].

All published reports to date have indicated significant diuresis and all have commented on the frequent gastrointestinal side effects as being the sole "toxic" manifestations[1,2,3,4,5]. No harmful sequelae have been observed, even in patients with chronic renal, cardiac and hepatic damage[3]. Nonetheless, the gastrointestinal symptoms have restrained usage of an otherwise potentially useful drug. The present study is based on the clinical trial of an enteric coated form of aminometramide† designed to obviate these effects.

Material and Methods. Two groups of male patients were studied. The first consisted of patients with chronic edema primarily noncardiac in origin. This group included 8 cases of portal cirrhosis with edema and ascites, and 2 in the nephrotic phase of glomerulonephritis. Those with cirrhosis all had received other diuretic therapy, with varying degrees of success, prior to this study. All the patients in this group were hospitalized throughout the entire program.

The second group was made up of 18 men drawn from an outpatient cardiac clinic. All had been on established weekly doses of from 1 to 4 ml. of mercurial diuretic. Diagnoses included arteriosclerotic heart disease, luetic heart disease, rheumatic heart disease, hypertensive cardiovascular disease, and chronic cor pulmonale. Throughout the study, these patients remained on the dosages of digitalis and on diets previously established. This group was followed only on an outpatient basis. Those who required hospitalization for any reason during the investigation were dropped from the study because of the many factors inherent in hospital care tending to promote circulatory efficiency.

A standard regimen of four 200 mg. tablets per day was selected. The medication was given with or shortly after meals and at bedtime with milk. Subjects who tolerated this dosage daily for varying periods were placed on increasing amounts of test material, up to 1400 mg. a day, regardless of the diuretic effect. Because of poor tolerance of the initial course a few patients were given a second course of 400 or 600 mg. per day.

Patients were used as their own controls.

*Present address: Medical Service, St. Luke's Hospital, San Francisco, California.

†The enteric coated aminometramide (Mictine) was made available by Dr. Irwin C. Winter, Director of Clinical Research, of G. D. Searle & Company.

After a period of observation, each patient, with the exception of the 2 patients with nephrosis, was given 2 ml. of mercaptomerin and the weight loss from this injection recorded. Enteric-coated aminometramide therapy was then begun after the subject had regained approximately the amount lost from the mercurial, and weights were recorded frequently. Upon the appearance of side effects, the ration was decreased, interrupted, or discontinued.

Insofar as possible, subjects were weighed in the same clothing at the same time of the day on the same scales and by the same individual. Care was taken to avoid suggestion of possible side effects.

Results. Table 1 is a summary of the entire series.

A. Eight patients with portal cirrhosis:

Two of these patients (B.F. and F.M.) were unable to tolerate the drug in small doses for over a week; the latter had a 15½ pound weight loss nonetheless.

One patient (O.S.) was unable to take 800 mg. per day, but tolerated 400 mg. per day without weight loss.

C.V. and H.B., who responded to mercurials with 2½ and 3 pound weight loss, lost 11 pounds each on 800 mg. Mictine daily and maintained the loss for the 20-day test period.

Two (M.M. and P.Q.), who had no apparent response to the mercurial, lost 16 pounds and 6 pounds respectively with no side effect.

One who responded to mercaptomerin with a 1½ pound loss, gained 2 pounds in 13 days with doses up to 1000 mg. per day.

B. Two patients with nephrosis:

One showed gradual weight gain on doses of 800 and 1000 mg. per day totaling 5½ pounds. Nausea was noted after 19 days, and the drug was discontinued.

One showed no response to doses of 800 and 1000 mg. for 20 days. Two days after institution of 1200 mg. dose, diuresis began and the patient lost 23 pounds in the ensuing 5 days. When clinically free of edema, the drug was stopped; he then lost 5 pounds more and remained stable. It is likely that this diuresis was spontaneous rather than induced, although there was no evidence either way.

C. Eighteen patients with heart disease and congestive heart failure: Four failed to lose weight or maintain a dry weight. Two of these took the medication only briefly because of the early appearance of gastrointestinal symptoms. A third failed to lose weight on the control injection as well. The remaining failure gained 2½ pounds on a 15-day trial at 800 mg. daily. This man's previous diuretic requirement was 4.0 ml. of mercaptomerin weekly. Five lost weight or maintained dry weight with concomitant gastrointestinal distress. One of these (T.R.) lost 9 pounds on his first 4 days of the program; after he was rested, side effects vanished, and he lost the newly accumulated 4 pounds in the next 5 days. Dry weight was subsequently maintained until the drug was discontinued because of side effects at a higher dose.

Another (P.L.) refused further trial after 13 days and 10½ pound weight loss. A third (G.B.) also refused after 4 days and a 4 pound weight loss. F.J. lost 4 pounds in his first 5 days but noted anorexia at the end of this time. After a brief rest, he was given two subsequent brief courses of a higher dose which were surprisingly well-tolerated considering the initial response. The

fifth, W.J., was unable to tolerate the standard dosage for more than 2 days. It was observed that these side effects ordinarily occurred well after the major diuresis, suggesting that an intermittent schedule might be advantageous.

The remaining 9 subjects lost weight and maintained dry weight on a specific dose without side effects, although, ultimately, increased dosage usually produced them in this group.

changes in the disease process not appreciated over a brief period of observation. Technical errors were certainly limited, since the only technical procedure consisted of weighing the patients.

It is to be noted that 9 patients at no time experienced anorexia, constipation, nausea, or vomiting; the other 19 did have some of these symptoms but in only 3 were they present throughout the administration of the drug. As elsewhere mentioned, however, the dosage

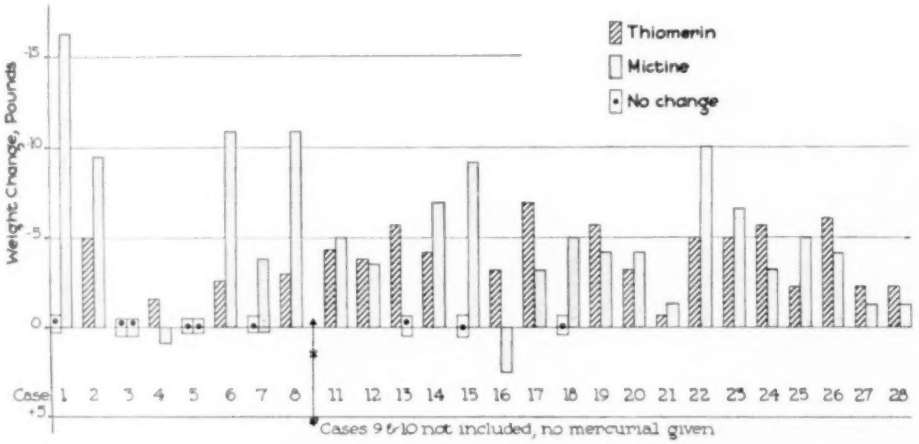
Thiomerin
Mictine
No change
Weight Change, Pounds
15
10
5
0
Case
1 2 3 4 5 6 7 8 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
+5
Cases 9 & 10 not included, no mercurial given

Fig. 1.—Diuretic response to Aminometramide as compared with the response to 2 ml. subcutaneous dose of Mercaptomerin. Cases 1 through 8 represent patients with portal cirrhosis and 11 through 28 represent ambulatory patients with congestive heart failure. Cases 9 and 10 were patients with nephrotic syndrome to whom mercurials were not given.

Figure 1 shows the total weight loss achieved on aminometramide therapy compared to the loss from the control injection of mercaptomerin.

Comment. Drug evaluation in humans is often deceptive, particularly in subjects not under complete hospital or laboratory control. Insofar as possible, sources of error were held to a minimum, but possible errors could result from; 1) failure of the patient to take the medication properly or at all, 2) weight loss due to gastrointestinal side effects, and 3) subtle

was carried to tolerance in nearly all cases regardless of diuretic effect. Thus interpretation of the toxicity data here indicates that a sufficiently large dose over a sufficiently long time may produce gastrointestinal disturbances. The average toxic dose for continuously administered drug was about 800 mg. daily. These gastrointestinal symptoms subsided abruptly with the withdrawal of the drug in all patients but one cirrhotic, who experienced anorexia for 3 days. No severe vomiting was seen.

TABLE 1.—SUMMARY OF PRESENT STUDY

Case No.	*Initials*	*Sex*	*Age*	*Diagnosis*	*Wt. Loss 2 ml. Mercaptomerin*	*Dosage of Drug mg./day**	*Days Trial*	*Weight Change*	*Previous Hg Maintenance Dose ml./wk.*	*Remarks*
1	M.M.	M	66	PC	0	800	13	−16	0	
2	F.M.	M	66	PC	5	800	5	− 9½	0	Anorexia, nausea, vomiting—rested 5 days
						400	9	− 6		Anorexia, nausea, vomiting—discontinued
3	O.S.	M	53	PC	0	800	3	0	0	Anorexia, nausea, vomiting—rested 4 days
						400	11	0		
4	F.K.M.	M	57	PC	1½	800	8	+ 1	0	
						1000	5	+ 1		
5	B.F.	M	61	PC	0	800	3	0	0	Nausea—discontinued
6	C.V.	M	57	PC	2½	800	25	−11	0	
7	P.Q.	M	69	PC	0	800	39	− 6	0	
8	H.B.	M	80	PC	3	800	16	−11	0	
9	G.W.	M	33	N	–	800	7	+ 1	0	
						1000	14	0		
						1200	7	−23		
						0	2	− 5		
10	J.M.	M	47	N	–	800	7	+ 2½	0	
						1000	19	+ 3		Anorexia, nausea, vomiting—discontinued
11	F.H.	M	81	ASHD	4½	800	5	− ½	2	
						1200	16	− 4½		Anorexia—rested
						1400	8	0		Anorexia, constipation, nausea, vomiting—rested
						1200	3	0		Anorexia, constipation, nausea, vomiting—
						0	3	− 3		Dry weight discontinued
12	J.G.	M	76	ASHD	4	800	7	− 2	4	
						1000	6	− 3½		
						1200	12	− 4		Nausea, vomiting after reaching dry weight
13	R.S.	M	63	ASHD	5½	800	3	0	2	Anorexia
						1000	4	0		Nausea—refused; maintained dry weight
14	P.L.	M	60	HCVD	4	800	9	− 7	2	Nausea, vomiting—rested
						800	4	− 3½		Nausea, URI—discontinued at dry weight
15	T.R.	M	55	LHD	0	800	4	− 9	4	Anorexia, nausea, vomiting—rested
						800	5	− 4		Anorexia, nausea—rested
						800	5	0		Constipation; dry weight
						1000	7	− ½		Nausea
16	S.M.	M	65	RHD	3	800	5	0	4	
						800	10	+ 2½		
17	J.W.	M	76	ASHD	7	800	15	+ 1	2	
						1000	16	− 3		Nausea, vomiting, weakness

18	P.A.	M	65	ASHD	0	800	7	0	3	
						1000	6	− 5		Anorexia
						1200	10	− 1		Occasional nausea
19	G.B.	M	77	ASHD	$5\frac{1}{2}$	800	4	− 4		Anorexia, nausea; refused
20	F.J.	M	68	ASHD	3	800	5	− 4	2	Anorexia
						1000	4	0		Anorexia, nausea—rested
						1000	7	$-2\frac{1}{2}$		Nausea
21	C.F.	M	72	HCVD	$\frac{1}{2}$	800	2	− 1	2	
						1000	12	0		
						1200	22	$+\frac{3}{4}$		Maintained dry weight
22	M.B.	M	54	ASHD	5	800	6	− 4	2	
						1000	4	0		
						1200	18	−10		Dry weight maintained
23	J.D.	M	66	ASHD	5	800	9	$-6\frac{1}{2}$	3	
						1000	3	− 1		
						800	7	$-1\frac{1}{2}$		
						1000	13	0		Nausea; maintained dry weight
24	F.D.	M	60	ASHD	$5\frac{3}{4}$	800	3	− 3	2	Anorexia, insomnia
						600	5	+ 3		
						600	6	$-2\frac{3}{4}$		Constipation
						800	6	0		Anorexia, nausea, vomiting
						1000	4	0		
25	J.W.	M	57	CP	$2\frac{1}{4}$	800	8	− 5	1	Constipation, nausea, vomiting—rested
						800	25	$-3\frac{1}{2}$		Anorexia; maintained dry weight
26	A.M.	M	62	ASHD	6	800	7	− 4	2	
						1000	2	$+1\frac{1}{2}$		Nausea, vomiting—rested
						800	7	$-\frac{1}{2}$		Anorexia—rested
						1000	4	− 1		Anorexia, nausea, vomiting
27	E.R.	M	63	ASHD	2	800	5	− 1		
						1000	8	0		
						1200	3	− 1		Anorexia, nausea, vomiting; dry weight
28	W.J.	M	58	ASHD	2	800	2	− 1	1	Nausea, vomiting—rested
						800	2	$-\frac{1}{2}$		Nausea, vomiting

ASHD :—Arteriosclerotic Heart Disease
PC :—Portal Cirrhosis
N :—Nephrosis
HCVD :—Hypertensive Cardiovascular Disease
LHD :—Luetic Heart Disease
RHD :—Rheumatic Heart Disease
CP :—Cor Pulmonale

* Drug given continuously unless otherwise specified

No other side effects or evidence of electrolyte imbalance were seen.

Conclusions. 1. Despite the small group tested over a brief period, it would appear that aminometramide is a promising diuretic, and may be effective where others are not. This appears to be particularly true in patients with portal cirrhosis and ascites.

2. Side effects, while of frequent occurrence in this series, were usually observed in supratherapeutic doses, or an appreciable length of time after diuresis appeared. It should be stressed that this was not a therapeutic but a test situation.

3. It may be inferred from this study that with an individually tailored regimen consisting of an interrupted and broken dosage schedule of no more than therapeutic amounts, enteric-coated aminometramide may provide a safe and useful addition to the diuretic armamentarium. It does not appear to derange acid-base equilibrium or afford the occasional risks of mercurials.

Summary. 1. Enteric-coated aminometramide was administered to 9 edematous patients with portal cirrhosis, 2 in the nephrotic state, and 18 members of an outpatient cardiac clinic. Six patients with cirrhosis exhibited significant diuresis. One of the patients with nephrotic edema sustained quite dramatic diuresis which may well have been spontaneous rather than induced. Fourteen of the cardiac group lost edema or maintained dry weight during the study.

2. A high incidence of gastrointestinal symptoms was encountered, consisting of anorexia, nausea, vomiting, or constipation. These were minor in degree, and usually followed high doses or long periods of administration. No harmful side effects were seen in patients with chronic hepatic, renal and cardiac disease. No particular correlation was noted between diuretic efficiency and symptoms of toxicity.

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SUMMARIO IN INTERLINGUA

Effectos Therapeutic e Toxic de Aminometramido in Forma de Enterico

1. Aminometramido in forma de enterico esseva administrate a 8 patientes con cirrhosis portal, a 2 patientes in stato nephrotic, e a 18 patientes visitante del clinica cardiac. Sex patientes con cirrhosis exhibiva significative grados de diurese. Un del patientes con edema nephrotic experientiava un diurese multo marcate que pote ben haber essite spontanee plus tosto que inducite per le droga. Dece-quatro subjectos in le gruppo cardiac perdeva edema o manteneva lor peso sic durante le curso del studio.

2. Esseva observate un alte frequentia de symptomas gastro-intestinal. Illos consisteva de anorexia, nausea, vomito, o constipation. Le grado de iste symptomas esseva minor. Usualmente le symptomas sequeva alte doses o prolongate periodos de administration del droga. Nulle nocive effectos lateral esseva observate in patientes con chronic morbos hepatic, renal, e cardiac. Nulle correlation specific esseva observabile inter le efficacia diuretic e le effectos toxic del droga.

THE RATIONALE FOR PSYCHOTHERAPY WITH OLDER PERSONS*

By Alvin I. Goldfarb, M.D.
Chief, Department of Psychiatry and Neurology, The Home for Aged and Infirm Hebrews, New York, New York

About 6 years ago neuropsychiatric rounds on a regular basis were initiated in the busy dormitories and infirmaries of a home for aged persons. At first the resident physicians led the writer most often to neurological cases, not so much because of their individual medical need but because of their nuisance value to staff and other residents. Members of the staff, the patients' families, or other residents of the Home appeared so troubled in conscience, guided by affection or impelled by mounting resentment as to demand that "something be done" for, or about the troublesome or suffering elderly person. Medical attention to the patient seemed to relieve guilty feelings, increase pride, re-establish confidence and augment alertness in the attendants, the family and the friends of the ill person. The improvement in their outlook was often the obvious reason for a reciprocal moderation of behavior in the disturbed person that occurred after only one or two visits. In this therapeutic institutional setting certain other observations were made which led to more elaborate efforts along psychotherapeutic lines with elderly people. The very ill, chronically disabled and brain-damaged old persons paraded few evidences of resources for the restoration of pleasurable interests. The enjoyment of food, controlled muscular action, socialization, sexual or intellectual activity are major satisfactions upon which self-esteem rests. The development of such pleasures and of pride in self seemed blocked by reduced and waning sensory, digestive, muscular, endocrine and cerebral cortical as well as general integrative and homeostatic powers. In addition, their financial and social resources were limited by their ways of the past and the ways of the world; and often their characters had been sadly deformed early in life, so that there was limitation of ability and loss of personal charm long before one of the complexes of ills we know as the syndrome "old age" had come along. In word or attitude, directly or indirectly, openly or by implication, they managed to convey the thought (like Arnold's Empedocles) that

> "He, who has outliv'd his prosperous days,
> Whose youth fell on a different world
> From that on which his exil'd age is thrown,
> Whose mind was fed on other food, was train'd
> By other rules than are in vogue to-day,
> Whose habit of thought is fix'd, who will not change,
> But in a world he loves not must subsist
> In ceaseless opposition, be the guard
> Of his own breast, fetter'd to what he guards,
> That the world win no mastery over him;
> Who has no fellow left, not one;
> Who has no minute's breathing space allow'd
> To nurse his dwindling faculty of joy—
> Joy and the outward world must die to him. . . ."

In the face of the massive problem presented by the ill, suffering, unhappy aged persons one could not avoid developing feelings of hopelessness and frustration. The psychiatrist was being called upon to evaluate the need for,

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and to decide on special handling, medication or disposition for difficult patients. With patients who presented such a discouraged and discouraging façade, who had "so little time," while the psychiatrist too had little time for them, he could not be entirely enthusiastic, vigorous or confident in attempting a conventional psychotherapy. Rather, despite feelings of futility, he tried to seek out and deal with whatever complaints were present in whatever way might suggest itself as momentarily helpful. In this, to discover the most prominent causes of distress, he quickly came to see the wisdom of following the associational trends of the patient as well as his presentation of the seeming facts. The associational trends often served to delineate the bodily ill, environmental irritation or personal problem that called for attention.

To the writer's surprise, his own self-assessment as to his potential helpfulness ran counter to the fundamental views of the patients, and were not accurate premonitions of the results. The attempts to understand the patients' complaints and to define their needs, whether productive of actual tangible service or a dismal failure in this regard, did appear to yield unexpected therapeutic results in many of the persons seen. Confusion of mental state decreased, vehement and angry displays abated, tearfulness and sadness diminished and disabling symptoms were ameliorated after the brief histories were taken, the rapid examinations done, the evaluations made and prescriptions given, often even before the medicines were taken or could have acted. These elderly patients, despite gross differences in reaction type, in the extent of brain damage and physical disability, despite differences in the duration of illness and in their characters previous to the onset of the particular symptom complex that constituted their aging; these differing elderly persons were reacting in notably similar ways. They tended to respond to, and interact with the examiner in obedient, compliant, defiant and angry combinations of attitude such as are well known in psychotherapeutic relationships, the development and examination of which can be so useful in intensive psychiatric treatment. They regarded the doctor with great trust or suspicion, delegated to him great responsibility or were guarded and cautious with him, expected great results from his attentions or tried to defend themselves from his malevolent influence; in short, they imbued him with great powers. Their ingratiation, resentment, coercive attitudes or placations all indicated that overtly or covertly they were of the opinion that this momentarily interested person would do them great harm or could do wonderful things for them if they could maintain his concern for their welfare. They had elected the physician to the role of parental surrogate, had "parentified" him. In a few cases this occurred with the trust, confidence, ease and immediate evidence of pleasure which seem to be a part of that early socially acquired and automatized "give and take" we know as affection. Here pleasure appeared to be generated by the formation of a friendship, and little else needed to be done. This was rare. In others, the fear of dealing with a powerful parental surrogate appeared to have an organizing effect leading to improved behavior; the fear of the delegated parent-surrogate in others led to anger which had an organizing effect followed by improved behavior. But even in these persons who had flights into health or flights from illness or change of symptoms to socially more acceptable forms, there were discernible elements of a more complicated process.

The following formulation of the process which occurred was useful as an operational concept. The person with diminished resources, both on old psychological and recent socio-psychophysiological grounds, is one who finds it increasingly difficult to master everyday problems and to satisfy everyday needs. Such failures result in loss of self-esteem. Each new failure or disappointment leads to increasing awareness of helplessness and ever increasing fears of more failures and of damage. There follows a search for help and for protection which adds to the loss of dignity. Meanwhile the fear further decreases resources through its disorganizing effects. Many variations of reaction stem from this point onward; some persons feel guilt for the burdensome role they believe themselves to be playing, others develop anger at the world which seems so harsh and hostile from their viewpoint of weakness and isolation. For many, the feeling "I am old and no good" becomes translated into "I hurt" and this sense of pain leads to suspicions of not being well cared for, of being neglected. This inverted awareness of needing help may lead to the exaggeration, exploitation or aggravation of existent and newly developing ills or to physically unwarranted complaining as a means of guaranteeing care, or of fending off desertion or neglect. Of course such motives are most often hidden from the environment and from the person himself. Equally well hidden from himself, and as much as possible from the environment, is his resentment of those persons regarded as neglectful and the anger he feels toward himself for his weakness and failures. The complaining, querulous, angry, pleading, ingratiating or frantic patient is therefore in need of assistance toward a feeling of increased worth, self-esteem or capability. Any maneuver which can encourage and reinforce the conviction that he is capable of mastering problems, especially those of social relationships, fosters a sense of pride and dignity, while ameliorating fear and removing the stimuli that give rise to anger. If in a personal relationship the person feels his need for understanding, respect, punishment, forgiveness, protection or the like is recognized and will be or is being served, he feels he has mastered the problem of social relationships which underlies his distress. Under these circumstances two features are of paramount importance. The first is that he feels it is through his own efforts, be these charm, wit, skill, or force of anger, that the service is won. Second, is the belief that the delegated parental figure has been acquired as an ally. Patients are thereby enabled to leave an interview with a victorious triumphant feeling, with a conviction of having a strong protector, or both. Thus strengthened their fear decreases, their anger fades, they are socially more acceptable, more self-respecting and more capable of productive behavior. Hereafter even small successes tend to breed further confidence with increasing, maintained or reinforcible gains in performance.

The rationale for psychotherapy of disturbed and disabled aged persons rests upon the assumption that their behavior is goal-directed, motivated, problem solving. If we subscribe to this view we need not feel discouraged about attempting psychotherapy even where the capacity for enjoyment, for sexual pleasure, or intellectual activity seems limited by physical limitations. When aged persons are viewed as actively attempting to solve present problems even though it is being done inefficiently, with poor psychological and emotional tools, and by means of emphasis on their own loss of resources, their very use of the dependency pat-

tern may be turned into a resource. So long as the observed behavior can be construed as having bearing upon the maintenance of some form of interpersonal relationship, the behavioral trends can be modified by using this motivating force for leverage. When the patient can be assisted toward the illusion that he has achieved success in manipulating, controlling, dominating or directing persons around him he has been assisted toward a satisfaction. The gratification obtained is biological in that it is an achievement of mastery over the environment and has an accompanying pleasure such as goes with problem solving and accomplishment of any kind. Some may call this "Nature's reward for utilitarian success", others may call is a "hedonic guide to survival", the writer tends to call it the affective tone of effective effector synthesis; whatever it is called, it is pleasurable, it is a gratification. In the therapeutic situation here outlined this gratification depends upon an illusion which is based on ontogenetic reality, cultural prolongation of the biological dependency period, and traditionally fostered legend that to hold power over a parental figure guarantees survival and pleasure. Under the best of circumstances, that of the infant in relation to its mother, this state of affairs constitutes only the first step toward the real satisfaction of most survival needs. The meaningful second step is the true provision of the wherewithal for survival and pleasure: food, protection and caresses. Achievement of the first step when the second is desired gives rise to pleasurable anticipation. When the pleasure of mastery permits a resting of action at the first step, and efforts repeatedly are directed toward this end (especially in persons who themselves are in some degree capable of realizing the acquisition of means for survival unaided) then we are justified in saying that an end has been made of a means. This propensity can be noted in countless variations in persons of any age all around us. Because it is so common in all age groups, and because it seems to be favored and brought out in circumstances of helplessness we find it, for our use, so frequently in the aged.

Here one should mention that the trend of the emotionally ill aged directly or indirectly to seek out and try to guarantee for themselves the services of now one, now another person is a reversal of the expectations of many younger persons in whom the same trends are prominently developed. They will consequently react to this behavior on the part of their elders as burdensome, and feel anxious or angry. Where the behavior is recognized for what it is, is understood, and does not threaten the personal requirements of those who care for the aged, this trend can be utilized in therapy, as has been elaborated. A healthy grasp of this problem by institutional or other attendant personnel is a great assistance toward success with the procedure described.

As a discouraging addendum it may be added that the efficacy of psychotherapy with the aged as outlined here is not universal. We feel that it has an ameliorative effect in about one-third, a stabilizing effect in about one-third and no good effect in the remainder of psychoneurotic persons with or without brain syndrome. It is, however, relatively ineffective in the psychoses. Where brain syndrome is very severe it is usually less effective, other factors being equal, than where it is mild; but it is well worth trying even where brain damage appears to be severe because the partial clearing of confused states with psychotherapy seems to us a demonstrable fact.

Summary. The efficacy of psychotherapy in the aged can be explained in a variety of ways. The very title of this paper underlines that our need to

treat older persons may be an important contribution to our results. The implication of diagnostic observation and treatment is interest and a desire to help; these tend to enhance self-esteem, especially where the older person can feel he has contributed to and brought out this concern through his own attributes or efforts. In its healthiest form this constitutes a capacity to form a relationship in which affection is pleasurably present. In the absence of affectionate capacity, this constellation appears as a manipulative controlling relation of patient to doctor in which the physician permissively or actively encourages the growth of victorious feelings in the patient. The arousal of pleasure with successful feelings constitutes a satisfaction in the purposive human of sufficient magnitude to perpetuate interest and activity. The trend is to further this state with the physician and possibly others. Propensities toward excessive struggle and angry behavior are damped by the sense of guilt which accompanies the victory and which can be subtly enhanced by the physician when required. The importance of this operational concept is that it permits active productive psychotherapeutic work along consistent lines with patients who might otherwise be regarded as being unable to achieve any satisfactions or pleasures and, therefore, as being incapable of benefiting from psychotherapy.

SUMMARIO IN INTERLINGUA

Argumento del Psychotherapia in Individuos de Etate Avantiate

Le efficacia del psychotherapia de individuos de etate avantiate pote explicar se de varie manieras. Le titulo mesme de iste articulo sublinea le facto que le urgentia de nostre desiro de tractar patientes de etates avantiate es possibilemente un importante factor in le realisation de nostre resultatos. Le justification e le base del observation diagnostic e del tractamento es le interesse del observator e su desiro de adjutar su patiente. E iste interesse e iste desiro tende a avantiar le respecto de se mesme del parte del vetule patiente, specialmente si ille pote creder que su proprie qualitates e su proprie effortio ha contribuite al disveloppamento del attitude de interesse e sympathia del parte de alteros. In su forma le plus favorabile, iste constellation resulta pro le patiente in le possibilitate de formar un relation affective in que ille trova un fonte de satisfaction. Si le patiente non possede un tal capacitate affective, le constellation resulta in le disveloppamento de un relation gerential inter patiente e medico, *i.e.* un relation in que le medico ha le function de permitter o de stimular activemente le generation de sensationes victoriose in le patiente. Le experientia de successo representa in le individuo human (con su horror del vita sin proposito) un satisfaction de grado sufficiente a perpetuar su interesse e su activitate. Le patiente se effortia a promover iste situation in su relation con le medico e possibilemente con alteros. Omne propension del parte del patiente a ingagiar se in excessos de combattivitate e de irascibilitate es amortite per su senso de culpabilitate que accompania su experientia de victoria e que pote esser subtilemente reinfortiate per le medico si un tal procedimento pare necessari. Le importantia de iste conceptiones de character dynamic e simultaneemente practic es que illos rende possibile un forma active e productive de psychotherapia secundo clar lineas de orientation in le caso de patientes qui alteremente poterea ben dar le impression que illes es incapace de attinger ulle grado de satisfaction e consequentemente que illes ha nulle prospecto de beneficiar del tractamento psychotherapeutic.

A COMPARISON OF THE METABOLISM OF RUBIDIUM 86 AND POTASSIUM 42 FOLLOWING SIMULTANEOUS INJECTION INTO MAN

By Malcolm P. Tyor, M.D.*
CLINICIAN

AND

James S. Eldridge, B.S.
ASSISTANT SCIENTIST

(From the Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission)

Although disturbances in potassium metabolism are recognized in a few disease states as evidenced by alterations in serum concentration or external balance, these data give no direct information concerning the body store of potassium. A total body deficiency of this cation may exist in the presence of a normal serum concentration[1]. The availability of radioactive potassium (K^{42}) has provided a method for measuring directly the total body content of potassium[5]. Although a few clinical studies with K^{42} have been reported[1,2,5,6], widespread use of this isotope has been limited by its physical characteristics (half life of 12.4 hours).

The possibility that rubidium may replace potassium in a biological system was first suggested by Ringer in 1887[15]. Since then, a number of investigations have confirmed their biologic similarity[4,7,8,9,11,12,13,21].

The physical characteristics of radioactive rubidium (Rb^{86}, 19.5 day half life) are suitable for tracer studies in human beings. The distribution of Rb^{86} in man has been reported upon[20].

The present report deals with the comparative radioassay of K^{42} and Rb^{86} in plasma, red cells, and urine, following their simultaneous injection into 5 patients.

Materials and Methods. SUBJECTS. Five patients, who were similar only in their uniformly poor prognosis, were studied. The pertinent clinical data are shown in Table 1. The patient's activities were not restricted in any way other than that indicated by their individual clinical state.

PLAN OF EXPERIMENT. The primary objective of the present experiment was to compare the relative proportion of radioactivity contributed by K^{42} and Rb^{86} in each sample of plasma, red cells, and urine. It was, therefore, necessary to plan the dosage of the two isotopes in terms of obtaining multiple samples for comparative counting over as long a period of time as possible. We were interested in possible differences in the metabolism of rubidium that might arise as a result of administering varying amounts of the stable component, since previous work with other isotopes, which also were not normal body constituents, showed significant alterations in metabolic behavior when the stable component was varied[10,16]. It was also planned to continue the collection of samples for Rb^{86} counting over a period of 10 days. The limiting factors included the probable inadvisability of injecting intravenously in a one-minute period more than 2 mEq. of the combined potassium and rubidium, and the short half life and relatively low specific activity of K^{42}. Since the patients studied had a uniformly short life expectancy, and all but one (D.C.) had had or were to receive radiation in the therapeutic range, the amount of radioactivity delivered in the K^{42} and Rb^{86}

*Present address: Department of Medicine, Veterans Administration Hospital, Durham North Carolina.

mixture was not considered to be of major concern.

PREPARATION AND DOSAGE OF K^{42} AND Rb^{86}. The K^{42} was obtained as a service irradiation from Oak Ridge National Laboratory° in all instances but one; here the shipment was received after a special irradiation in the Low Intensity Training Reactor at Oak Ridge National Laboratory (specific activity of K^{42} increased by a factor of 15). All K^{42} was received as potassium carbonate. The Rb^{86} was obtained as a service irradiation from Oak Ridge National Laboratory° as rubidium carbonate.

Initial processing of both isotopes included their individual conversion to potassium chloride and rubidium chloride with 1.0 N HCl and boiling, adjustment of the pH to between 7 to 8, and dilution of each solution to 25 ml. to produce stock solutions with cation concentrations:

Sol. 1: Potassium 0.636 mEq./ml.
Sol. 2: Rubidium 0.225 mEq./ml.

An aliquot of each stock solution was then assayed for radioactivity. The final solutions included a mixture of the rubidium 86 chloride, potassium 42 chloride, and in 3 instances sufficient sodium chloride to give a total of 0.154 mEq. of cation per ml. For example, in patient D.C., it was planned to inject 0.25 mEq. of rubidium in a volume of approximately 10 ml. When the K^{42} received as a service irradiation was used, it was necessary to inject at least 0.5 millicuries, which contained approximately 1 mEq. of potassium, to obtain samples that would have significant counting rates over a relatively long period of time. The final cation concentration injected in this patient, then, was:

Potassium 42, 0.1 mEq./ml.
Rubidium 86, 0.025 mEq./ml.
Sodium, 0.029 mEq./ml.

In each instance, the final solution was autoclaved and injected intravenously over a one-minute period through calibrated syringes. The relative amounts of stable and radioactive potassium and rubidium administered to each patient are shown in Table 2.

COLLECTION AND PREPARATION OF SAMPLES. In all patients, 12 ml. of whole blood was withdrawn from a vein in the arm opposite to that of injection and was heparinized. Blood samples were obtained at varying time intervals in each patient, the earliest time of

TABLE 1.—CLINICAL DATA

Patient	*Age*	*Sex*	*Diagnosis*	*Remarks*
A.G.	83	M	Chronic lymphocytic leukemia.	Disoriented. Generalized lymph node enlargement. Hepatosplenomegaly. Hgb 10.0 gm., WBC 410,000.
E.C.	50	F	Adenocarcinoma of breast; pericardial and left pleural effusions.	Previous therapy with colloidal Au 198 injected into pericardial space. Receiving testosterone.
M.M.	72	F	Adenocarcinoma of thyroid with questionable small pulmonary metastases.	Previous complete thyroidectomy; euthyroid on desiccated thyroid. General condition good.
D.C.	12	M	Acute blast cell leukemia.	Febrile. Generalized lymph node enlargement, hepatosplenomegaly. Hgb 8.5 gm., WBC 4,500. Receiving 6 mercaptopurine.
G.G.	41	M	Malignant plasmocytoma.	Multiple osteolytic lesions.

TABLE 2.—RELATIVE AMOUNTS OF STABLE AND RADIOACTIVE POTASSIUM AND RUBIDIUM ADMINISTERED TO EACH PATIENT

Patient	*mc K 42*	*mc Rb 86*	*mEq. K*	*mEq. Rb*	*mEq. Na*
A.G.	0.45	0.26	1.04	1.05	1.13
E.C.	0.56	0.29	0.07	1.52	0.0
M.M.	0.45	0.26	1.03	1.04	1.12
D.C.	0.54	0.43	1.01	0.25	0.296
G.G.	0.55	0.32	1.04	0.14	0.42

°Isotopes Catalog and Price List, July, 1952, ORNL, No. 59.

sampling being 10 minutes and the latest 60 hours.

In 4 patients, each whole blood sample was immediately centrifuged at 3000 rpm for 20 minutes. Five milliliters of the supernatant plasma was pipetted into an 85 × 15 mm. culture tube and sealed for counting. An aliquot of unwashed red cells, from each sample, was then hemolyzed with distilled water and a hemoglobin determination was performed with a Klett-Summerson colorimeter. Five milliliters of the hemolyzed red cells were then delivered into a culture tube and sealed in preparation for counting. In one patient (A.G.), the heparinized whole blood was allowed to stand at room temperature for one hour. The plasma and white cell layer was then delivered into a calibrated centrifuge tube and spun at 3500 rpm for 25 minutes. The volume of packed white cells was measured. The plasma and red cells were then handled in a similar manner to that described previously. The white cells were digested with nitric acid and 5 ml. were pipetted into counting tubes.

Individual urine samples were collected from each patient. The volume of each specimen was measured and a 5 ml. aliquot was counted.

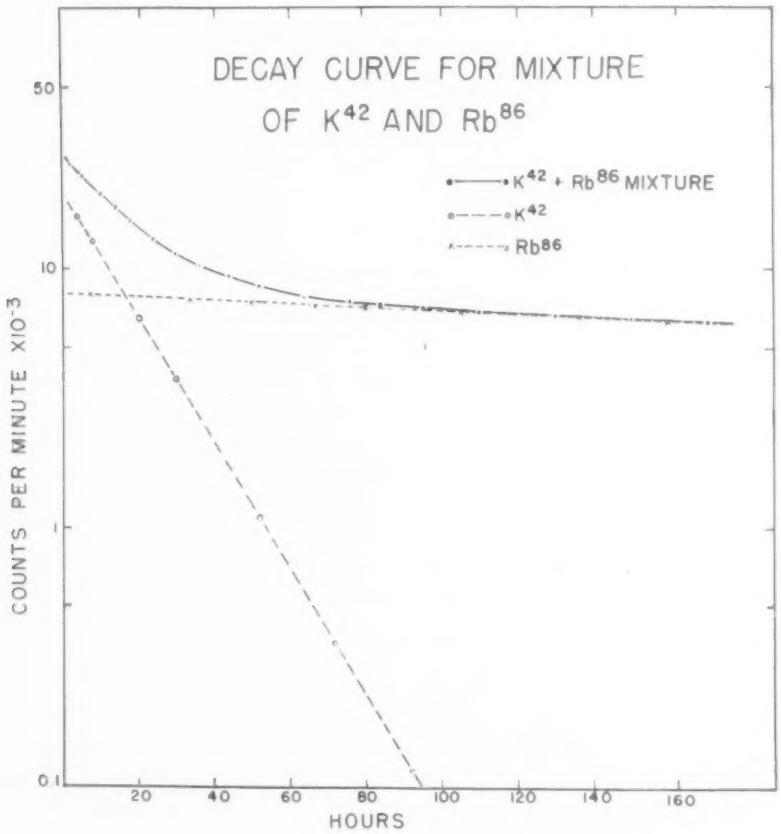

Fig. 1.

MEASUREMENT OF RADIOACTIVITY. All samples were counted with a "well" scintillation counter, containing a 1.5 inch sodium iodide crystal. The counting efficiency was 16.7% for K^{42} and 6.4% for Rb^{86}.

Each sample was counted twice. The first count was made within 3 hours after the sample was prepared. Following the initial count, the sample was allowed to decay for

5 days (K^{42} activity reduced to one-tenth of 1% of that of the first counting) and then recounted. The concentration of radioactivity obtained at the time of the second count was due to Rb^{86} alone. This value was corrected for decay to the time of the first counting, and the value obtained was subtracted from the concentration of radioactivity at the initial time of counting. The difference represented the radioactivity due to K^{42}. Both values (K^{42} and Rb^{86}) were then corrected for decay to "T_0" (time of injection) for purposes of comparison and analysis.

Multiple counts were obtained from a standard made from a dilution of the K^{42} and Rb^{86} mixture administered to each patient, and the relative amounts of radioactivity contributed by each isotope were calculated in the same manner as described previously (Fig. 1). The mean of the several values obtained for each isotope was calculated, and the relative amounts of each isotope injected were obtained from this value (Table 2 and Fig. 1).

We were not aware of the presence of a radioactive cesium (Cs^{134}, 2.3 year life) impurity in the Rb^{86} obtained as a service irradiation nor of the variations in counting efficiency of Rb^{86} and Cs^{134} with beta as compared with gamma measurements, until studies in the first 4 patients had been completed. Because of the relative abundance of beta and gamma energies emitted by the two isotopes, an average contamination of the Rb^{86} with Cs^{134} of approximately 0.5% is increased by a factor of 10 to 20, when a "well" scintillation counter is used. In each instance the original standard was counted over a 48-week period, and the contamination by Cs^{134} was calculated. This amounted to approximately 6.3% in patients A.G. and M.M., 9.3% in patient E.C., and 5.8% in patient D.C. Since the percentage of radiation due to the contaminant increases with time, the per cent error of this contamination was calculated in the late samples obtained from patient E.C. The maximum possible error was found to be 5%. This probably represents a considerable over-estimation of error, since studies on the relative metabolism of Rb^{86} and Cs^{134} suggest somewhat similar pathways of distribution[11,17,19]. The fifth patient, G.G., was then studied with Rb^{86}, which was free of Cs^{134} contamination, the cesium having been removed by ion exchange prior to the irradiation.

COMPUTATION OF DATA. The values for plasma and urine were expressed as counts per milliliter, the red cells as counts per gram of hemoglobin, and the white cells as counts per milliliter of packed cells.

The total counts in each sample were obtained, and the per cent count contributed by K^{42} and Rb^{86} was computed as follows:

1. $$\% \text{ total counts } Rb^{86} \text{ in sample} = \frac{\text{Counts } Rb^{86} \text{ in sample} \times 100}{\text{Total counts } (K^{42} + Rb^{86}) \text{ in sample}}$$
2. % total counts K^{42} in sample = 100 − % total counts Rb^{86} in sample. A ratio was then obtained from 1 and 2 and compared with a similar ratio obtained from the relative activities injected:
3. $$R_1 = \frac{\% \text{ total counts } Rb^{86} \text{ in sample}}{\% \text{ total counts } K^{42} \text{ in sample}}$$
4. $$R_2 = \frac{\% \text{ total counts } Rb^{86} \text{ injected}}{\% \text{ total counts } K^{42} \text{ injected}}$$

The difference in dosage between patients was corrected by the following ratio:

5. $$R_3 = \frac{\% \text{ total counts } Rb^{86} \text{ in sample}}{\% \text{ total counts } Rb^{86} \text{ injected}}$$

Results (Table 3). The per cent of total counts of Rb^{86} and K^{42} in each sample of plasma, red cells, and urine was relatively constant within each patient. When the ratio of Rb^{86} and K^{42} in the *plasma* and *red cells* of individual patients was compared with the ratio of the mixture injected, they were found to be similar. The ratio for *white cells* also agreed closely with that of the administered dose.

In contrast, the ratio of Rb^{86} to K^{42} in the *urine* of each patient was constantly lower than in the mixture injected. This was attributable to a slower excretion of Rb^{86} (Fig. 2). The lower values for the ratio of Rb^{86} to K^{42} in urine bore a consistent relationship to the ratio of the dose injected in each patient. The ratios (R_3) of per cent total counts Rb^{86} in urine to the per cent total counts Rb^{86} injected were similar in all patients ($\bar{d} = 0.58$; range 0.54 to 0.64; average S.D. = 0.065).

Comment. It is apparent from the comparative concentration of Rb^{86} and K^{42} in plasma, red cells, and white cells that the two isotopes have a distinctly

TABLE 3.—THE RELATIVE ACTIVITY OF Rb 86 AND K 42 IN PLASMA, RED CELLS, WHITE CELLS, AND URINE AS COMPARED WITH THE INJECTED DOSE

	Patient: A.G.				Patient: E.C.				Patient: M.M.				Patient: D.C.				Patient: G.G.			
	Period Observed (hours)	No. of Determinations	Mean	Standard Deviation	Period Observed (hours)	No. of Determinations	Mean	Standard Deviation	Period Observed (hours)	No. of Determinations	Mean	Standard Deviation	Period Observed (hours)	No. of Determinations	Mean	Standard Deviation	Period Observed (hours)	No. of Determinations	Mean	Standard Deviation
Plasma																				
% total counts/ml. Rb 86	43.5	8	17.6	2.58	48	7	13.2	1.94	48	8	15.8	3.13	24	4	23.2		44	8	9.6	1.00
% total counts/ml. K 42	43.5	8	82.4	2.58	48	7	86.8	1.94	48	8	84.2	3.13	24	4	76.8		44	8	90.4	1.00
R_1* $\frac{\%\text{ total counts/ml. Rb 86}}{\%\text{ total counts/ml. K 42}}$	43.5	8	.22	.037	48	7	.15	.025	48	8	.19	.035	24	4	.30		44	8	.11	.012
RBC																				
% total counts/gm. Hgb Rb 86	24	7	16.8	1.99	48	8	14.2	1.65	60	9	15.1	2.09	60	6	22.5	3.38	44	8	11.2	.84
% total counts/gm. Hgb K 42	24	7	83.2	1.99	48	8	85.8	1.65	60	9	84.9	2.09	60	6	77.5	3.38	44	8	88.8	.84
R_1* $\frac{\%\text{ total counts/gm. Hgb Rb 86}}{\%\text{ total counts/gm. Hgb K 42}}$	24	7	.20	.031	48	8	.17	.022	60	9	.18	.027	60	6	.29	.059	44	8	.13	.010
WBC†																				
% total counts/ml. Pw Rb 86	43.5	8	18.1	.56																
% total counts/ml. Pw K 42	43.5	8	81.9	.56																
R_1* $\frac{\%\text{ total counts/ml. Pw Rb 86}}{\%\text{ total counts/ml. Pw K 42}}$	43.5	8	.22	.009																
Urine																				
% total counts/ml. Rb 86	69	15	9.9	1.03	50	12	9.1	1.00	64	12	9.9	.87	45.5	18	14.7	1.38	42	14	6.5	.83
% total counts/ml. K 42	69	15	90.1	1.03	50	12	90.9	1.00	64	12	90.1	.87	45.5	18	85.3	1.38	42	14	93.5	.83
R_1* $\frac{\%\text{ total counts/ml. Rb 86}}{\%\text{ total counts/ml. K 42}}$	69	15	.11	.013	50	12	.10	.015	64	12	.11	.012	45.5	18	.17	.019	42	14	.07	.009
R_2* $\frac{\%\text{ total counts/ml. Rb 86 urine}}{\%\text{ total counts/ml. Rb 86 injected}}$	69	15	.57	.061	50	12	.64	.089	64	12	.57	.052	45.5	18	.60	.056	42	14	.54	.069
R_2* $\frac{\%\text{ total counts injected Rb 86}}{\%\text{ total counts injected K 42}}$			.21				.17				.21				.33				.14	

* Ratio (subnumerals correspond to computations on page 189.
† WBC determinations are expressed as milliliters of packed white cells.

similar metabolism. On the other hand, there is an obvious disparity in the urinary excretion of these isotopes. This difference is always due to a proportionately slower excretion of Rb^{86}. Furthermore this excretory pattern appears to be similar in all patients studied and is not altered by minor variations in the dosage of stable rubidium nor by age, sex, and the dynamics of the several diseases studied.

Burch and his associates have recently reported on the similarity of plasma concentrations of K^{42} and Rb^{86} from samples drawn during the first 2 hours after their simultaneous injection into 2 patients with heart disease, one of whom had congestive failure[3]. They have also noted the slower excretion of Rb^{86}, with an average ratio of the excretion of Rb^{86} to K^{42} of 0.52 and 0.68 in 2 subjects followed for 2 and 5 hours respectively[14]. These figures compare favorably with the present data and indicate little difference between the early and late excretion of the 2 isotopes.

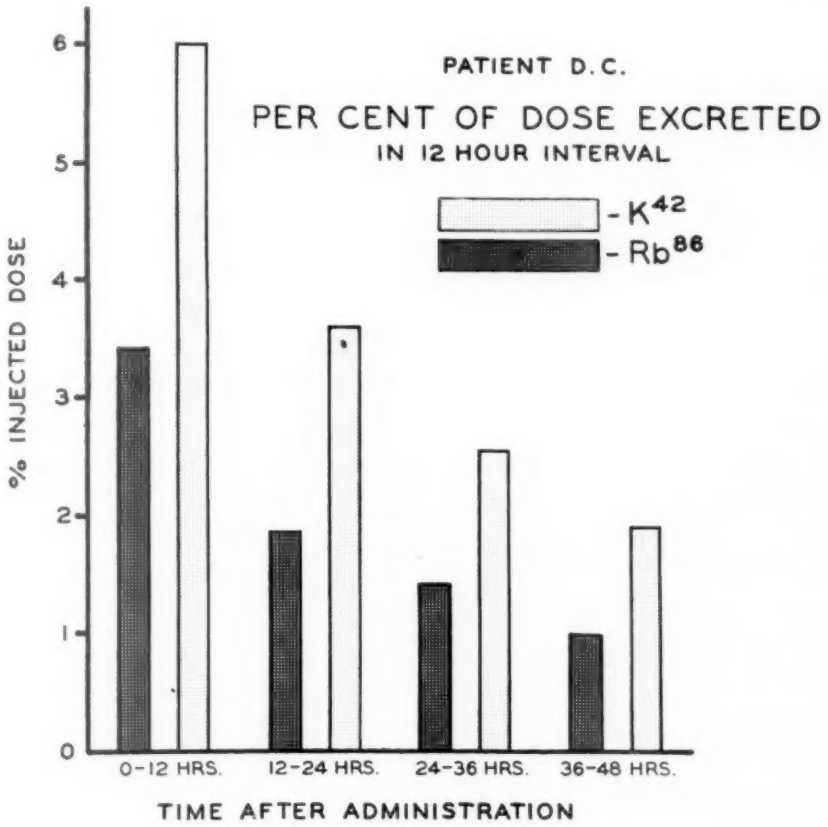

Fig. 2.

When Zwaardemaker[21] interchanged solutions containing potassium, rubidium, thorium, and radium and obtained similar recordings of heart muscle contractibility, he theorized

that this similarity in behavior was due to the naturally occurring radioactivity of these ions. Cesium, which is not a naturally occurring radioelement, produces a similar effect on heart muscle. Apparently rubidium, and to a lesser extent cesium, will replace potassium in a number of biological systems but with varying degrees of efficiency. Studies with Cs^{134} in dogs[17] and preliminary data in three patients, who were given simultaneous injections of K^{42} and Cs^{134} [19], confirms certain biochemical similarities of these ions. Present biological knowledge of the alkali elements does not afford a clear explanation of these observed similarities and differences. The first three members of this group (lithium, sodium, and potassium) are strikingly different in their biochemical behavior. It is difficult to explain the similarities of potassium, rubidium, and cesium through considerations of the relative mass of these ions.

The reliability of the values obtained from studies of space and mass are greatly enhanced by multiple samplings of a major intracellular compartment over a prolonged period of time[18]. Similar concentrations of K^{42} and Rb^{86} are present in red cells and white cells for 60 and 43.5 hours respectively. The presented data indicate that Rb^{86} and K^{42} have a similar metabolic behavior and that useful information concerning potassium metabolism may be obtained from long term studies with Rb^{86}. These data must be interpreted in light of the differences in urinary excretion of the two isotopes.

Summary. 1. Within individual patients a constant ratio of Rb^{86} and K^{42} in plasma, red cells, white cells, and urine was maintained throughout a 2 to 3-day period of observation.

2. The ratio was similar to that of the injected dose in all fractions except urine, which showed less Rb^{86} and more K^{42}.

3. The ratio of urinary excretion of the two isotopes had a definite relationship to the ratio of the injected isotopes and was similar in all patients studied (average 0.58).

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SUMMARIO IN INTERLINGUA

Comparation del Metabolismo de Rubidium-86 e Kalium-42 post Injection Simultanee in Humanos

1. In patientes individual un proportion constante de Rb^{86} e K^{42} se manteneva in plasma, erythrocytos, leucocytos, e urina durante un periodo de observation de 2 a 3 dies.

2. Le proportion esseva simile al proportion del doses injicite, in omne casos excepte le caso del urina que monstrava minus Rb^{86} e plus K^{42}.

3. Le proportion del excretion urinari del duo isotopos monstrava un definite relation al proportion del isotopos injicite e esseva simile in omne le patientes studiate (valor median 0,58).

SUMMARIO IN INTERLINGUA

(See page 119 for original article)

Ingestion de Salicylato: Un Causa Frequente de Hemorrhagia Gastric

Es reportate le casos de un gruppo de patientes qui exhibiva signos de hemorrhagia gastrointestinal superior post ingestion de salicylatos. Le casos esseva simile in tanto que le sanguination esseva sin dolor, que acido libere esseva trovate in le stomacho jejun, e que nulle prova roentgenographic de ulceres esseva obtenibile. Tres del patientes habeva habite numerose episodios de melena in le curso de multe annos. Le ingestion de aspirina semper precedeva le sanguination. Hypoprothrombinemia non esseva le causa del sanguination proque le tempores prothrombinic esseva normal in omne casos in que illos esseva determinate, e le quantitate de salicylatos ingerite non sufficeva pro deprimer significativemente le concentration prothrombinic del sanguine. Il es possibile que allergia gastric contra salicylato esseva responsabile pro le sanguination in le casos in que le hemorrhagias esseva frequente e extendite super longe periodos de tempore.

Le uso de salicylatos pare augmentar le frequentia de sanguination in patientes qui suffre demonstratemente con ulceres peptic. Le mechanismo del sanguination non es clar, tanto in le patientes qui suffre demonstratemente de ulcere peptic como etiam in le patientes qui ha ni symptomas ni provas laboratorial del presentia de ulceres peptic. Le causa es possibilemente un factor mucosal local, sed il es plus probabile que aspirina causa erosion peptic e sanguination per augmentar le aciditate gastric. Nos presenta le hypothese que le variation saisonal del frequentia del activation de ulcere peptic es possibilemente explicabile in parte per le plus frequente uso de iste droga durante le "mense ulceric."

Omne patientes con hemorrhagia gastrointestinal superior deberea esser questionate in re lor uso de salicylato o de drogas commercial que contine salicylatos. Iste mesura pote ben provar se un salva-vitas.

RESERPINE AS AN ANTIHYPERTENSIVE IN THE OUTPATIENT CLINIC: A DOUBLE-BLIND CLINICAL STUDY*

By C. T. Bello, M.D.
ASSISTANT PROFESSOR OF PHARMACOLOGY, ASSOCIATE IN MEDICINE AND CHIEF OF THE HYPERTENSION CLINIC

AND

Linton W. Turner, M.D.
INSTRUCTOR IN MEDICINE

(From Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania)

The purpose of this study was to evaluate various effects of oral reserpine on a group of hypertensive individuals in an outpatient clinic.

This and other fractions of the root of *Rauwolfia serpentina* have been used extensively in the treatment of hypertension and for emotional disturbances since their importation into this country from India began a few years ago. Reports of hypotensive properties of various fractions of *Rauwolfia serpentina* are numerous, but the impressions as to the degree of hypotensive action of these have been variable. For example, Chakravarty and Rai Chaudhuri[1] extracted an alkaloid with petroleum ether having a melting point of 235° C. These authors gave 20 mg. twice daily to 15 hypertensive patients and noted an average fall of 30.7 mm. Hg systolic blood pressure and 19 mm. diastolic blood pressure; the initial blood pressures of these patients ranged from 240/150 to 160/98. They further noted that several of their patients had shown transient nausea, fainting and dyspnea during treatment and recommended that it is "probably safer to start with half the dose for the first 1 to 2 days to guard against precipitous drop in blood pressure." Since the advent of use of rauwolfia alkaloids in the United States, recommended dosage schedules have been considerably lower. Wilkins and Judson[6], reporting on the use of a preparation of unstated concentration imported from the Himalayan Drug Company in Bombay, India, felt that rauwolfia was a moderate hypotensive agent especially useful in patients with hypertension and tachycardia and recommended its use in conjunction with more powerful drugs. More recently Corcoran *et al.*[2] conclude that the average daily dose of reserpine should probably be about 0.5 mg. or less and state, "The drug is a useful and potent agent in some patients with severe as well as mild hypertension."

Youngken[7] has made a botanical study of the rauwolfia roots which he has found in lots imported to the United States. In this work he has found a number of substitutes and adulterants in place of *Rauwolfia serpentina;* the most frequently found of these substitutes were: *R. canescens, R. micrantha, R. densiflora, R. perakensis* as well as occasional undetermined species.

The present general attitude toward the use of reserpine, then, appears to

*The Reserpine was supplied in the form of Serpasil by the Ciba Pharmaceutical Products Inc., Summit, New Jersey.

be that it is a potent antihypertensive agent alone or in combination with other drugs of value in cases of mild, labile hypertension.

Materials and Methods. Twenty-five patients who had been attending the Hypertension Clinic at Temple University Hospital for many months were selected. Twenty-three of these people were women and two were men. Of this group 17 were colored and 8 were of the white race. Their ages ranged from 31 to 73 years. All of these patients had been previously studied to rule out renal, neoplastic, or endocrinologic etiology of hypertension. Several objective base line studies were done: 1) blood pressure readings, 2) funduscopic examination with Keith-Wagener-Barker classification by a consulting ophthalmologist*, 3) electrocardiograms were done prior to and following completion of the entire study period. The patients were divided into three groups of 6 individuals and one group of 7 individuals and were rotated by groups through four successive programs each with a duration of 5 weeks. The programs consisted of the following: 1) no medication, 2) placebo, three times daily, 3) reserpine 0.2 mg. three times daily, 4) reserpine 0.5 mg. three times daily. The clinical method used was the double-blind approach with two of the investigators (L. W. T. and B. D.) always examining the patients and with the third (C. T. B.) always dispensing the drug prescriptions. The patients were instructed at the outset of the experiment not to discuss medication with the examining physician. Those individuals chosen for this trial were picked at random from the clinic group with mild to moderate benign essential hypertension who were not taking medication for any other related or unrelated disease process. The prescriptions contained numerical symbols to which only the clinic pharmacist held the key. The medications were physically identical, all being white tablets of approximately 0.5 cm. in diameter. Blood pressures were routinely taken by the same examiners (L. W. T. and B. D.) and were taken in both sitting and standing postures, though these are not recorded herein as there were no significant differences. Prestudy blood pressure determinations were gleaned from the clinic charts, which in many cases dated back several years. Finally, the rudiments of the trial were explained to the patients as their fullest cooperation was vital in motivating them to weekly visits over a time of 5 months.

TABLE 1.—AVERAGE FINDINGS IN THE 25 PATIENTS

Number of Patients	*Average Age*	*Average Blood Pressure*	*Average Pulse*	*Eye Grounds*	
25	51	175/105	81	Sclerosis	
				Grade I	7 patients (28%)
				Grade II	15 patients (60%)
				Grade III	3 patients (12%)
				Attenuation*	
				Mild	11 patients (44%)
				Moderate	6 patients (24%)
				Severe	3 patients (12%)

* Keith-Wagener-Barker Classification.

Results. The accompanying charted data are arithmetical averages of weekly determinations of pulse and blood pressures taken under the various stated circumstances. There were no unusually large fluctuations in blood pressure in either direction in the record of any patient. No consistent or significant changes in average blood pressures can be noted on any regimen as opposed to another. A rather slight lowering of pulse rate, similar on all study regimens, can be noted as opposed to the prestudy period. The slight trend toward improvement in several electrocardiograms cannot be attributed to lowering of blood pressure and may have been due to any one or more factors too numerous to mention. Since

*Dr. Arthur Vaughn, Jr., Department of Ophthalmology, Temple Hospital, Philadelphia, Pennsylvania.

there were virtually no differences in the arithmetical means of patients' blood pressures from group to group and inspection showed no particular difference in the distribution around the mean, it was not felt necessary to determine the standard error of the mean. It may be seen that these combined averages are virtually identical in regard to pulse rate of pretreatment period as opposed to any study regimen. The most obvious interpretation of this pulse change is that it is due either to 1) central sedative effects or 2) the calming effect of being treated vigorously with a new drug.

TABLE 2.—BLOOD PRESSURE READINGS BEFORE AND AFTER THERAPY

	Average Readings Prior to Study		*No Medication During Study 5 Weeks*		*0.2 mg. Reserpine TID for 5 Weeks Average Readings*		*0.5 mg. Reserpine TID for 5 Weeks Average Readings*		*Placebo 5 Weeks Average Readings*	
Name	*P.*	*B.P.*	*P.*	*B.P.*	*P.*	*B.P.*	*P.*	*B.P.*	*P.*	*B.P.*
1. I.B.	84	148/98	76	120/86	73	118/86	69	120/80	76	130/86
2. H.B.	85	180/96	76	148/76	65	146/94	72	128/87	84	175/114
3. F.W.	81	161/107	67	152/103	68	148/96	73	163/98	68	150/96
4. M.S.	65	215/122	61	222/122	60	221/117	61	245/105	74	190/105
5. N.S.	89	178/106	75	185/108	70	190/103	76	205/108	72	190/98
6. M.D.	84	182/114	70	187/109	65	198/102	66	206/104	73	200/114
7. B.K.	73	156/100	60	145/100	62	143/85	63	147/90	64	143/85
8. P.S.	76	176/110	60	165/104	62	164/100	71	169/95	68	180/106
9. K.A.	82	163/97	64	146/92	70	149/92	66	134/79	72	132/84
10. D.B.	86	162/110	68	146/102	63	153/104	65	162/108	68	144/98
11. M.B.	76	170/105	75	176/112	70	185/115	70	158/102	71	170/114
12. E.W.	92	175/110	90	180/128	94	168/120	83	189/125	87	185/123
13. A.R.	90	170/110	70	165/112	62	136/88	70	124/85	65	115/90
14. M.D.	74	197/108	70	170/106	66	180/102	72	194/112	82	185/106
15. M.B.	73	166/95	72	170/100	70	168/98	70	172/100	74	168/94
16. E.W.	84	154/94	76	163/94	71	158/94	70	159/90	70	145/80
17. M.W.	85	177/120	66	177/113	66	175/118	62	197/114	64	185/110
18. F.D.	82	170/94	76	202/107	62	192/102	74	181/96	85	205/120
19. R.C.	68	180/110	61	210/115	62	202/120	59	210/118	58	190/115
20. B.B.	84	182/97	64	160/90	72	160/100	64	166/104	76	175/101
21. V.S.	86	190/102	74	185/100	73	208/105	67	226/110	76	212/115
22. L.W.	81	194/104	75	200/110	65	212/112	71	203/106	67	210/106
23. G.T.	92	180/120	69	185/105	66	175/105	69	213/114	70	200/115
24. M.W.	82	160/102	70	172/102	71	170/108	65	170/100	65	150/100
25. F.L.	76	186/106	69	192/103	67	187/104	73	207/122	62	177/92
Average	81	175/105	70	173/104	68	172/103	69	180/102	72	172/103

Side effects consisting of muscular aches and pains (6 patients), stuffiness of the nose (6 patients), drowsiness (4 patients), headaches (one patient), nausea and vomiting (one patient) occurred in the above order of frequency and numerical incidence. About two-thirds of the patients had some form of side-effects while taking reserpine at either dose level, while about one-third of the patients experienced no side-effects whatsoever. No individual experienced side-effects of the above nature while on any regimen beside the reserpine therapy. We regard this as reasonable inductive evidence that the reserpine was absorbed.

Discussion. Negative results of this study are not a denial of the clinical usefulness of rauwolfia in many patients. The psychological make-up of the individual may be quite important in determining the response to any drug or stimulus. The kind of personality and the type of emotion are mixed in the hypothalamus to determine the

form of the discharge[3]. It will not be surprising then, if a drug which is effective in the highly strung executive who is treated as a private patient in the private office, hospital or at home responds in a different manner from the more phlegmatic ambulatory patient in the free outpatient clinic. This is especially true since reserpine is known to modify various vasomotor reflexes[4] by central inhibition of reflex pressor sympathetic activity[5]. For instance, treatment which is begun in the hospital[2] is often effective and as was demonstrated in these studies the same drug in an outpatient situation may prove to be largely ineffective.

Summary. A controlled clinical study of reserpine was carried out on 25 ambulatory clinic patients known to be mildly to moderately severe hypertensive individuals. The drug had no significant effect on pulse or blood pressure. Side effects were reported by approximately two-thirds of our patients. The importance of the environment of the patient in contributing to results with rauwolfia therapy is discussed.

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SUMMARIO IN INTERLINGUA

Reserpina Como Antihypertensivo in le Clinica de Patientes Visitante Studio Clinic Duple-Occulte

Esseva executate un controlate studio clinic de reserpina in 25 patientes de clinica visitante con cognoscitemente leve a moderate grados de hypertension. Le droga habeva nulle significative effecto super le pulso o le pression sanguinee. Effectos lateral esseva reportate per circa duo tertios de nostre patientes. Nos discute le importantia del ambiente del patiente como factor contributori al resultatos del therapia a rauwolfia.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.
JOHN RHEA BARTON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

AND

C. G. JOHNSTON, M.S., M.D.
PROFESSOR OF SURGERY, WAYNE UNIVERSITY
DETROIT, MICHIGAN

CURRENT CONCEPTS CONCERNING THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

BY ROBERT T. CROWLEY, M.D.

(From the Departments of Surgery of Wayne University College of Medicine, Detroit, Michigan, Detroit Receiving Hospital and Veterans Administration Hospital in Dearborn, Michigan)

ALTHOUGH considerable and even dramatic advances have been made, particularly in the last decade, there is as yet no specific therapeutic agent for pulmonary tuberculosis. Consequently, concepts as to treatment of the disease are in a state of gradual but continual change. They are likely to remain so for some time to come, or at least until the awaited specific curative agent is synthesized or discovered.

It is of considerable importance to the physician to be fully aware of the current trends in treatment of pulmonary tuberculosis. This is true for the reason that he is likely to encounter the disease frequently and unexpectedly whatever his particular pursuit or specialty. The importance of such familiarity is further emphasized by certain statistical facts presently holding:

1) Tuberculosis is still the chief cause of death from communicable disease throughout the entire world, accounting for approximately 5,000,000 deaths annually.

2) An estimated 40,000 to 45,000 deaths occur annually in the United States from the disease, the death rate being about 22 per 100,000.

3) The ratio of active cases to deaths from tuberculosis is about 10:1. Thus there are probably in the region of 500,000 active cases currently in the United States.

4) Tuberculosis is still the greatest cause of death in the age period between 15 and 35 years[16].

A sound, practical familiarity with

the current concepts of therapy and their possible future advancements is considerably facilitated by an examination of the various phases through which therapeutic concepts have evolved to the present day.

The rational therapy of tuberculosis probably dates from the discovery of the tubercle bacillus by Koch in 1882[52, 53]. Before this the principal contributions to study of the disease in living subjects were in the form of two procedures which facilitated detection of its presence and progress. These procedures were percussion, originated by Auenbrugger in 1716, and stethoscopic auscultation begun and developed by the French physician Laennec in 1819.

Shortly after his discovery and demonstration of the tubercle bacillus as the causative organism of tuberculosis, Koch produced the tuberculin reaction subsequently to be of considerable aid in the diagnosis of the disease. In that year, 1884, recognition of the achievements in the treatment of the disease by Charles Trudeau culminated in the institution of the first sanatorium devoted exclusively to the care of tuberculosis patients at Saranac Lake, New York[80].

Trudeau's essential concept of the therapy of tuberculosis was basic. Its essential postulate was that the disease, whatever its stage, was essentially a symbiotic condition existing between the organism and host, and that its progress of decline depended upon the balance between the virulence of the infection, and the resistance of the infected subject. Quite logically he reasoned that since the organism could not be destroyed by any means within the body, that the therapeutic effort could best be directed toward strengthening or improving the resistance of the host. This resistance, he further reasoned, could best be effected by complete systemic and local rest. The patient's physical activity was rigidly limited. More or less complete bed rest and a full measured diet were the essential elements of the Trudeau regimen of treatment. The considerable success attending these measures was duly noted and gradually accepted as the general practice in the treatment of the disease. Their efficacy is attested by the fact that they are in use as an integral part of therapy of the present day[80].

Some 11 years later a tremendous impetus to both diagnosis and management of pulmonary tuberculosis was given by the discovery of Roentgen ray by Wilhelm Roentgen. Until that time, 1895, detection of the disease and knowledge of its progress or regression were dependent upon the extant clinical signs, such as weight loss or the presence of fever, and physical findings elicited by percussion and auscultation. With the advent of Roentgen ray and its subsequent refinements an extremely potent implement was made generally available by which early detection of the disease and estimation of response to treatment could be accurately determined.

While Trudeau's concepts of tuberculosis therapy were effective and generally accepted, they were at best indirect, consisting as they did in making the therapeutic effort almost entirely toward increasing the resistance of the host by complete rest and making no direct attack on the lesions of the disease or their causative organisms. With the advent of Roentgen ray and its rapidly evolving techniques for determining the location and extent of pulmonary lesions, therapeutic efforts could now be made directly against the lesions themselves.

Here, too, the therapeutic concept was a furtherance of the objective of complete rest of the diseased part by directly immobilizing the diseased

lung to promote the healing of its lesions. Since the pulmonary manifestation of tuberculosis may be protean in type and stage of progress, a variety of procedures were developed and practiced to achieve this common end. These procedures are generally designated as collapse therapy.

Before considering the various forms of collapse therapy it is perhaps at point to indicate more specifically the general effects by which collapse or reduction of lung volume promotes beneficial results in the diseased parenchyma.

When the volume of the diseased lung is effectively reduced by whatever means, there is a general tendency toward the healing of its extant lesions by fibrous encapsulation with or without attendant calcification of the healed areas. This tendency toward healing is brought about by the relaxation incident to the collapse of the elastic properties of the lung parenchyma which in the expanded state provides a natural resistance to scar formation. The elastic properties of the lung also account for the so-called "selective collapse" sometimes observed when the lung volume is reduced. In such instances the diseased areas, if they contain fibrotic tuberculosis foci, undergo greater collapse than the surrounding uninvolved parenchyma because of the difference in elastic gradient between the diseased and uninvolved tissue. Actual cavitary disease and extensive areas of caseation, however, rarely, if ever, show the phenomenon of selective collapse with moderate degrees of reduction of lung volume. In these lesions, practically complete pulmonary collapse may be required for obliteration[4,19,36,57,58,68,77,78].

A further therapeutic effect of collapse and lessening of lung volume is the reduction of lymphatic flow in the contracted lung parenchyma and the reduced ventilation in the pulmonary segments as well as contraction of the segmental bronchi. These effects of collapse lessen the likelihood of lymphatic and bronchogenic spread of the disease[4,78].

The obliteration and healing of parenchymal lesions were and currently remain the most frequent aim of collapse therapy and the most frequent indication for its use. The success attending collapse therapy in cavitary tuberculous disease depends upon the type of cavity and its location. Such lesions have been broadly classified and correlated according to the effect collapse is likely to exert[4,77,78].

1) Those cavities in caseo-cavitary disease with little or no limiting fibrous wall and found in areas of exudative reaction. Cavities of this type are likely to be resistant to any form of collapse therapy employed unless the entire lung is collapsed.

2) Those cavities which have little or no limiting fibrous wall and little or no surrounding parenchymal reaction. This is the form of cavity best suited to obliteration and healing by collapse therapy of any type.

3) The last cavitary type is that possessed of an extremely thick limiting fibrous wall and which characteristically does not collapse under relatively high pressures. This is the most difficult of all cavitary lesions to obliterate due to its resistant fibrous wall. It is likely to persist whatever collapse procedure is employed.

The effects of collapse in cavitary disease of any type are mediated in general by a threefold process: The first is by relaxation of the fibrous strands radiating from the cavitary wall through the parenchyma and pleural reflections. These fibrous radiations tend to keep the cavity open by traction on the wall and their release therefore allows coaptation of the walls. Second,

when such fibrous radiations are released there is an inherent tendency of the fibrous tissue of the wall to contract concentrically and further coaptation of its walls. And third, the progressive granulation of the coapted cavity walls tends to further and complete its obliteration. Thus the net effect of the above factors exerted by collapse is the release of distending elements, coaptation of the walls, and obliteration by fibrosis[4,19,77,78].

The effect of collapse on cavitary and other tuberculous lesions is, however, not the only consideration in its employment. The general effect of collapse on the uninvolved or normal pulmonary parenchyma must be taken into account. These effects are variable, depending on the presence or absence of intercurrent complicating factors during the period of collapse. If this period is not complicated by infection, or its sequelae, the underlying parenchyma and its capacity for re-expansion may be little affected. There the lung may then properly re-expand with little functional loss. In such instances a slight functional loss occurs by restrictive adhesions between the parietal and visceral pleura of the completely expanded lung. In the event, however, of hydrothorax or infection, such as empyema, intervening during the period of induced collapse the capacity of the lung for re-expansion may be greatly limited on discontinuance of reversible collapse therapy. This may occur because of increased fibrosis of the pulmonary parenchyma but the more important element in the prevention of lung re-expansion is usually the formation of a restrictive organized fibrous layer of variable density over the visceral pleura of the atelectatic lung parenchyma. In such instances the surgical removal of the fibrous layer is likely to be required before any degree of re-expansion can be obtained. These considerations concerning the effect of collapse on normal lung tissue obviously obtain only in instances where the form of collapse therapy is designed for temporary or reversible collapse of the diseased lung, such as pneumothorax, phrenic nerve crush, or pneumoperitoneum. Where some form of permanent collapse treatment is employed such as thoracoplasty they are of considerably less import[19,57,58,77,78].

As pointed out above, the pulmonary lesions of tuberculosis are protean in location, extent, and stage of development. It is not surprising, therefore, that no single form of collapse therapy can be universally applied to all forms and phases of the disease. The various types of collapse therapy must be evaluated in terms of the various manifestations of the disease. One form of collapse therapy may be very efficacious in one type of tuberculous lesion and wholly inadequate in another. Some lesions may yield to practically any form of collapse treatment while others may be refractory to any form. The problem in collapse therapy is thus by and large the decision as to which individual form of collapse therapy will produce the greatest therapeutic effect in a given type of lesion. It is a matter of general knowledge that since the advent of excisional therapy for tuberculous lesions there has been a steady decrease in the practice of collapse therapy of all types. Indeed, many of the individual forms of collapse therapy have been thereby rendered practically, if not entirely, obsolete, though in the occasional case they may seem to be indicated. Among the reasons for the steady decline in collapse therapy and the advance in excisional treatment is the fact that the various forms of excisional treatment may be more universally applied to the various manifestations of the disease. However, this may be, some familiarity with

the individual forms of collapse therapy is necessary if the reasons for the gaining popularity of excisional treatment is to be properly understood. On this account the individual collapse procedures more frequently employed in the past are subsequently recalled.

Artificial pneumothorax as a possibility for the treatment of pulmonary tuberculosis was mentioned in the early part of the 19th century by Carson[15] although there is no record of his having actually utilized the procedure. Actually it was not until almost a hundred years later, under the impetus of its use and advocation by Forlanini in 1882[32] and Murphy[69] in 1898, that it began to be widely popularized. It continued as a preferred form of treatment until the recent past and is still practiced by some in occasional selected cases. From the time of its inception until the present, a considerably body of factual data has accumulated allowing a reasonable retrospective evaluation of its use.

Theoretically it is an ideal form of collapse therapy for several reasons. The entire lung can be subjected to its effects at one time allowing selective collapse if possible to occur. It is a reversible form of treatment which allows the possibility of lung re-expansion following healing or stabilization of the parenchymal lesions. Bilateral pulmonary lesions may be treated concurrently still allowing sufficient lung function to permit the patient some activity. It is nondeforming. It is generally easily induced and controlled and may avoid more drastic surgical forms of intervention entirely. On the other hand, there are adverse considerations in its use. It can be employed under ideal circumstances in only about 20% of cases requiring therapy. It is not the most effective of collapse procedures and many lesions are not improved by its use because adequate collapse cannot be achieved. When this occurs, considerable crucial time may be wasted which might have been put to a more effective form of collapse treatment. Even when adequate collapse is obtained, periods of from 2 to 4 years are likely to be necessary before the lung can be allowed to expand without jeopardizing the effect. The possible untoward results are not inconsiderable. Pleural effusion and consequent fibrosis with loss of function of some degree occur in over one-half the cases. Tuberculous empyema arises some time during the course of collapse in 20% of subjects. The lung fails to re-expand in 5 to 10% of treated cases. There is a mortality of 1 to 3% recorded[64,66,77,92].

Aside from the disadvantages cited above, the use of artificial pneumothorax is limited by certain contraindications which are common concomitants of tuberculosis. Pleural symphysis or fibrotic adhesion of the visceral and parietal pleural layers of any considerable degree will prevent adequate pneumothorax collapse. Tension cavities cannot be obliterated by its use. Exudative lesions, stenosing bronchitis, extensive pulmonary destruction, tuberculous pleuritic effusion, and severe dyspnea incident to emphysema or cardiac disease are all commonly occurring possible conditions which may preclude its use. It may be noted in passing that these same considerations generally apply to the employment of oleothorax, first used and advocated by Bernau in 1922[8]. This consisted, as the name suggests, in the injection of oil into the pleural cavity instead of air to achieve collapse. Because of its obvious disadvantages it did not attain wide use and has long since been abandoned.

Moreover, even when pneumothorax has been employed as the selected form of collapse therapy, complicating features may arise which demand its discontinuance. Uncontrollable dyspnea

may occur. The affected lung may develop lobar atelectasis and repeatedly collapse spontaneously, or accumulate persistent pleural effusion. There may be associated pleural adhesions which are not amenable to severance or thoracoscopic visualization may have revealed subpleural tubercles. Thus, by the development of intercurrent factors such as the above, any pneumothorax collapse, although long in progress, may have to be terminated as rapidly as possible[77,92].

Early in the development and practice of artificial pneumothorax as a form of collapse therapy, it was recognized that a fair number of cases might well respond to the procedure if intrapleural adhesions present could be eliminated[77,92]. These were cases in which the fixative fibrous bands between the visceral and parietal pleurae were of such number and strength that the affected lung or some of its segments were mechanically fixed in a distended position. There being no other contraindicating circumstances, elimination of the mechanical distending effects of these adhesions would permit adequate collapse by subsequent artificial pneumothorax. Accordingly there developed with the practice of artificial pneumothorax the supplemental procedures of pneumonolysis to permit the successful employment of pneumothorax[28,33,50]. All pneumonolysis procedures are designed for the release of limiting adhesions to permit adequate collapse. The procedures of pneumonolysis may be either open or closed. In open pneumonolysis the limiting adhesions are directly visualized and severed by open thoracotomy. This method of open procedure was advanced by Friedrich as early as 1911[33] and the closed method subsequently strongly advocated by Eloesser in 1926[28].

The most frequently used technique for pneumonolysis, however, was the closed intrapleural approach carried out with a thoracoscope by which the restrictive adhesion could be directly visualized and severed. This technique, originated and reported by Jacobeus and sometimes referred to as the Jacobeus operation[50] was attended by large success. This is reflected in the reports of Day, Chapman and O'Brien[23] in a large series of reviewed cases. By this method a complete collapse was obtainable in 50% of cases and partial but satisfactory in 42%. The pneumothorax was finally discontinued in 30%. The attendant mortality of the procedure was between 1 and 2%[23]. The principal contraindications to the use of the method were largely those extant for collapse therapy; generally extensive pleural effusion or empyema, widespread underlying parenchymal disease, very extensive adhesions over giant cavities (4 cm. or greater), and prohibitive extents of pleural adhesions[23]. Aside from these complications the use of closed intrapleural pneumonolysis was further limited by complications incident to the process: empyema, intrapleural hemorrhage, extensive subcutaneous emphysema, bronchopleural fistula, and loss of the pneumothorax incident to the latter[23].

Various other methods of producing pneumonolysis have been devised and practiced, aside from those just described, as supplemental measures to aid in collapse by pneumothorax. At this juncture it is at point to contemplate them briefly alhough they are rarely employed in current therapy.

These are the various techniques designed generally under so-called extrapleural pneumonolysis[6,26]. All such procedures involve separation of the chest wall from the bony support of the ribs to allow collapse of the soft tissue against the underlying pleural cavity and lung. The resultant space between the ribs and the collapsed

chest wall may then be filled with some substance to aid in maintaining the collapse. Depending upon whether the chest wall is separated from its rib support by separating the visceral from the inner aspect of the intercostal musculature or by separation of chest wall including visceral pleura, intracostal musculature, and periosteum as a single layer, pneumonolysis is designated extrapleural or supraperiosteal in type. Tuffier[102] first employed extrapleural pneumonolysis in 1893. In his original technique the resulting space between ribs and chest wall was not filled with any substance to maintain the collapse. Later in 1901, Sarfert[86] advocated filling the space with gauze to aid collapse and since that time a wide variety of substances have been employed for the purpose. Tuffier in 1910[102] filled the space with fat and somewhat later Baer[6] endeavored to accomplish the same purpose with paraffin as the agent.

Considerably later, supraperiosteal pneumonolysis came into use to accomplish the same purpose. Lillenthal[60] initiated the procedure in 1928 of performing the procedure utilizing gummed sheeting to fill the space between the denuded ribs and the chest wall. Thereafter Eloesser[29] in 1932 employed paraffin and Alexander[2] in 1934 accomplished the same end with attached muscle grafts. A wide variety of substances have been assayed and advocated for this purpose. Most recently the insertion of lucite spheres into the defect has been employed[109].

The difficulty inherent in either extrapleural or supraperiosteal pneumonolysis combined with space-filling foreign substances is that such substances, whatever their nature, are prone to shift in position and thereby become less effectual in collapse maintenance. Moreover, since all such devices are actually foreign bodies, their presence very greatly increases the likelihood of infection of the space necessitating their subsequent removal[14,62,72,99]. In any event, all such pneumonolytic procedures have in the last decade become progressively more obsolescent with developing excisional techniques.

During the time that artificial pneumothorax and its supplemental procedures of pneumonolysis were progressively being advanced and practiced a wholly different method of achieving therapeutic collapse became recognized and widely employed[3]. This was by temporary or permanent interruption of the phrenic nerve. The use of this procedure clinically was originally stimulated by the work of Stuertz in 1911[95] who proposed using phrenic nerve paralysis to attain diaphragmatic elevation and collapse of diseased lower lobes. According to Alexander[3], Sauerbruch, in 1913, reported in 3 cases in which the procedure had been carried out clinically. He advised supplementing the operation with thoracoplasty for additional collapse when needed. Almost simultaneously in the same year, 1913, Mellin, Kroh and Felix[3] made the clinical observation that occasionally the diaphragm was incompletely paralyzed even when the main phrenic trunk was divided. This phenomenon was explained by Friedrich[34] in 1914 on the basis of the presence of accessory phrenic nerve fibers which if allowed to remain intact, continued to function and thereby prevent total diaphragmatic paralysis. At this time, also, Friedrich advocated crushing rather than division of the phrenic nerve to produce temporary instead of complete paralysis. Subsequent to this contribution, various authors, notably Goetze[38] and Felix[31] in 1922, emphasized the importance of dealing with accessory phrenic fibers when present to achieve adequate collapse by the method. The procedure

grew in popularity and a considerable literature has arisen in conjunction with its use[3].

The rationale underlying all surgical interruptions of the phrenic nerve for collapse purposes, whether by severance, crush, or extirpation, is that the resultant paralytic elevation of the diaphragm markedly reduces the volume of the affected pleural space and allows the lung to collapse to that extent. Phrenic nerve interruption has been strongly recommended by many as the first collapse procedure to be considered in those cases requiring surgical intervention of any type[3].

Certainly it has been widely practiced but its popularity, like all other forms of collapse therapy, has rapidly lessened since the advent of excisional surgery. In any event, certain adverse considerations are inherent in its use and the resultant diaphragmatic paralysis reduces pulmonary function to a very marked degree. It renders coughing considerably less effectual; it allows paradoxical mediastinal shift affecting the capacity for ventilation of the opposite lung. For this latter reason it is contraindicated in instances where thoracoplasty may be ultimately required. In such, phrenic paralysis may dangerously increase the amount of paradoxical respiration incident to the thoracoplasty. Further, there is no question that paralysis of the left diaphragm induced by left phrenic nerve interruptions may precipitate frequent and stubborn persistence of a variety of gastrointestinal symptoms. Further, the possibility of failure of the lung to re-expand must always be borne in mind in temporary interruptions (phrenic crush). In approximately 10% of such instances, though all precautions have been exercised, the lung will remain permanently collapsed. In spite of the above limiting considerations, surgical interruption of the phrenic nerve may be carried out to advantage under the following possible indications. It may be used in instances of minimal lesions to augment or supplement the healing promoted by a bed rest regimen. It may be utilized in reactivations of old fibrotic lesions which show no cavitation. It can be employed in basilar lesions which show no cavitation. It can be employed in basilar lesions persisting after attempts at collapse thoracoplasty. It may be considered as an adjunct procedure in instances of small cavities (3 cm. or less) which have remained unobliterated by pneumothorax, and it may be used as a supplementary procedure in certain instances of re-expanding pneumothorax[3,5].

It is perhaps appropriate to mention two other procedures developed to promote collapse therapy, the use of which became general. These procedures attempted in 1942[3] and 1926[5] were scalenotomy and intercostal neurectomy. As the name implies, the former was designed to obtain some collapse of the chest wall by severance of the scalene muscle fibers close to their costal attachments, thus allowing the apex of the thoracic cage to fall away from its normal position. The second was intercostal neurectomy by which a collapse of sorts was obtained by section of the intercostal nerve, thereby producing paralysis and retraction of the internal and external muscular components of the chest wall. Little need be said of these procedures except that because of the inadequate collapse produced and their limited application both as definitive or supplemental procedures, they were never widely employed and have long since become obsolete. They are, however, of some historical import in that they exemplify the general interest at the time in various methods which might be employed to obtain therapeutic collapse[3].

Until the advent of the concept and practice of excisional treatment of tuberculosis, thoracoplasty was the most widely applied form of collapse therapy. It still remains so. Indeed even with the sudden and considerable adoption of excisional methods of treatment many prominently qualified opinions currently hold that modern thoracoplastic techniques offer a sound form of treatment of pulmonary tuberculosis[3]. Because of the retained importance of thoracoplasty in the current treatment of tuberculosis it is of advantage to recall the essential stages in the evolution of this foremost form of collapse therapy.

DeCerenville of Lausanne[25] is credited with the first attempt to provide collapse by removal of costal segments of the thoracic cage in 1885. His early attempts, while producing collapse of some degree, had very limited success because the rib resection was not sufficiently extensive. Gourdet[39] some years later in 1894, by extending DeCerenville's limited localized rib removal conclusively demonstrated that a greater reduction of the volume of the thorax and hence a greater degree of collapse was obtainable when short paravertebral rib segments were removed than when segments of comparable length were excised anterolaterally. This significant observation demonstrated the increased effective collapse when rib segments were excised medial to the rib angles and as far posteriorly as the transverse processes of the vertebrae. In 1907, Brauer[10,11], in an effort to extend effective collapse, advocated the removal of entire rib segments from ribs two through nine inclusive, a technique that was adopted and regularly practiced by Friedrich beginning in that same year[33].

In 1909, Sauerbruch[88,89] began the performance of a paravertebral thoracoplasty with the removal of ribs one to eleven inclusive. Before and after this time, 1907 to 1913, Brauer[10,11] and Friedrich[33] performed a more or less routine one-stage resection of ribs two through nine inclusive by what came to be designated as "subscapular paravertebral thoracoplasty." In 1911 Wilms[108] further confirmed clinically the experimental observations of Gourdet[39] by doing 4 cm. resections of ribs paravertebrally and obtaining effective collapse. Dating from this year, Wilms and Sauerbruch, working independently, each modified the technique of the Brauer-Friedrich thoracoplasty[88,89,108] by resecting ribs nine and ten and by removing somewhat longer segments of the other ribs than Wilms had done previously. This modification of Wilms' original technique became known as the Wilms-Sauerbruch paravertebral thoracoplasty. The essentials of this technique were a restriction of the excision to the paravertebral portions of the rib and resection of the first rib included. It is of interest to note that Sauerbruch began the procedure at the lower ribs of the thoracic cage and proceeded upward to the first[88,89,108].

With the increasing use of thoracoplasty as a collapse technique, further refinements were added. In 1924, Lambert[55] advocated removal of the upper rather than the lower ribs at the first stage of any thoracoplastic procedure, and this practice became generally adopted.

In 1925 Hedblom[45,46] urged the multiple stage thoracoplasty as a precaution against the paradoxical movements of the chest and mediastinum as well as a possible precaution against dissemination or spread of the disease incident to the procedure. At this time also, Alexander[1] began removing increasingly greater rib segments in multiple stages. Thus, following 1925 the collapse procedure of thoracoplasty had

become more or less standardized into a technique in which great lengths of ribs and the conjoined transverse processes were removed in stages from above downwards with maximal collapse results. This ultimate thoracoplasty technique is that employed currently in collapse therapy[70].

The considerable body of clinical literature which has accumulated concerning the use of thoracoplasty as the foremost of collapse procedures has more or less well established its indications, contraindications, complications and associated mortality[3,70,74,96,97].

In instances which may be benefited by thoracoplasty several general features are requisite. The lesion should be unilateral or in the instance of bilateral lesions, the contralateral lesion should be stable. In such cases it is far better if the lesion on the side for which thoracoplasty is contemplated is also stabilized lessening the chance of subsequent spread. It is also mandatory that the subject have adequate pulmonary function with a sufficient margin of reserve. This is true for the reason that effective thoracoplastic collapse of the affected side will considerably reduce respiratory function. In addition, the patient should be out of the normal growth period since in the young the procedure is likely to be extremely deforming due to concurrent bone growth. Ideally also the patient should be under the age of 50 before the degenerative fibrotic and emphysematous changes incident to age have advanced in the pulmonary parenchyma. The limitations of thoracoplasty as a therapeutic procedure are not inconsiderable and can perhaps be best appreciated by indicating the various conditions which may absolutely or relatively contraindicate its use[33,70,96].

Absolute contraindications exist in the form of uncontrollable disease on the contralateral side, inadequate pulmonary reserve, severe nontuberculous disease such as cardiac lesions which may render any surgical procedure hazardous, endobronchial tuberculosis, and cavities which by reason of their thick walls or location cannot be collapsed by the procedure. Relative contraindications may also exist in the form of severe exudative tuberculosis, bronchiectasis, and epithelialized cyst-like cavities or so-called tension cavities unlikely to be affected by thoracoplastic collapse. Two possible complications incident to thoracoplasty have been considerably reduced by improvement in technique and the routine use of antibiotics. They are of necessity to be considered in conjunction with the likely result of the procedure. Wound infection, as with any operation, is always a possibility. Paradoxical respiration is an extremely frequent complication. When this occurs the question of its degree is of major import. Where the mobility is slight the subject suffers little danger or inconvenience. When marked, death may result because of cardiovascular embarrassment and there may be an increased disposition to the endobronchial dissemination of the disease. Untoward effects due to its incidence may be largely prevented by properly staging the procedure and when it does ensue may be treated by adequate immobilization of the decostalized chest wall[3,70,74,96,97].

Whether paradoxical respiration occurs or not, endobronchial spread of the disease may take place. This complication is to be assiduously avoided for the associated mortality of such spread has been recorded as high as 33 1/3% in subjects not having received antibiotic therapy[56]. With adequate antibiotic treatment this mortality is undoubtedly far lower. Aside from these immediate complications, later possible sequelae must be pondered. There is always some degree of reduction of pul-

monary function. This dysfunction is the result not only of the collapse of the lung on the operated side but to some degree due to the dysfunction incident to the scoliosis which affects the contralateral side. It is estimated that following the usual seven rib thoracoplasty the reduction of pulmonary function in the over-all, as reflected by the maximal breathing capacity, may range from 15 to 35%[79]. The importance of this possible effect need not be emphasized. Thoracoplasty is inevitably attended by some degree of deformity since it is essentially a mutilating procedure. Scoliosis occurs in spite of prolonged postoperative physiotherapy for its prevention. This scoliosis is likely to be extremely marked in children during the growth period and has the peculiarity of convexity of the spine toward the affected side. The reason for this direction of the convexity has never been wholly elucidated although a possible explanation lies in the dyssymmetry the thoracoplastic procedure creates in the action of the opposing muscles attached to the first and second ribs and the anterior rib segments. In any case, the scoliosis, as noted elsewhere, reduces pulmonary function in the sound lung[3,56].

There are besides the scoliotic component of thoracoplastic deformity a marked disability and disfiguration of the shoulder girdle on the affected side. This disfiguration is characteristically an infraclavicular depression. On elevation of the shoulder joint, an inward and medial rotation of the scapula occurs in combination with the scoliosis already noted. This deformity of the shoulder not infrequently limits abduction of the arm. But more important is a type of disfiguration or deformity which is easily noticeable. On this account, because of the unfortunate cosmetic result, the procedure of thoracoplasty is refused by many subjects. It is at point to add that the deformity is likely to be considerably increased when partial scapulectomy is performed subsequent to the thoracoplasty. Further, with or without scapulectomy some degree of deformity is incident to thoracoplasty although proper physiotherapy may accomplish much to minimize it[3,56].

As with any surgical procedure the value of thoracoplasty is weighed in terms of possible risks involved against results achieved. The operative mortality approximates 5 to 7%[3,79]. There is an over-all mortality in the region of 20%. About 75% of cases pass into the stage of arrested disease while in 5% the process remains active. The best results are obtained in cases with fibrous or fibro-caseous disease, while the poorest are obtained in those with giant cavities or marked parenchymal destruction as would be expected. These statistics are based on 3- to 4-year follow-up studies and represent reasonable approximates[79]. In a larger series followed for longer periods, 5 to 15 years, the following statistical observations, also probably reasonable approximates, have been recorded[73]: an over-all mortality of 27%; sputum converted to negative and remaining so, 85%; clinically cured, 50%. Sixty-six per cent considered themselves cured and carried on full time occupations. Twelve per cent were able to engage in part time work[73].

As has been indicated, the success of thoracoplasty is likely to be limited in certain types and locations of tuberculous lesions. These lesions are primarily of the cavitary type. Thus there have developed various procedures which are used in conjunction with thoracoplasty to further the collapse obtained by thoracoplasty and augment cavity closure. By and large, these supplementary procedures are of two general types: cavity drainage

techniques and plombage procedures to attain additional lung collapse. While the attainment of more specific forms of collapse was the primary objective of these procedures, other considerations entered into their employment. They were done in an attempt to avoid the deformity inherent in the performance of thoracoplasty. They have been used in patients whose lung functional status is so doubtful that conventional thoracoplasty is not feasible. And they have been advanced as compromise therapy completed in one stage where the assumption of mortality and morbidity risks of multi-staged operations does not seem warranted.

The supplemental procedures have already been briefly indicated in conjunction with collapse therapy by pneumothorax (*vide supra*). Latterly, however, their most frequent use has been as adjunct or compromise therapy relating to thoracoplasty; in other words, either to supplement or substitute for thoracoplastic collapse. These procedures fall into three general types: intrapleural, that is, pneumothorax, extrapleural pneumonolysis with plombage, and supraperiosteal pneumonolysis with plombage (*vide supra*). These procedures as a whole are far from ideal because all of them involve the creation of intrathoracic dead space filled with foreign bodies of some nature placed there to maintain collapse. The very presence of the foreign body increases the probability of infection, which, should it develop, necessitates removal. The interposed foreign bodies of which there are many types, are very difficult to maintain in exact position of original placement and are inclined to shifting or wandering from optimal sites. Again, the interposition of foreign bodies between the thoracic wall and the underlying soft tissue of necessity creates pressure against the latter which is likely to cause varying degrees of pressure necrosis of the tissue with consequent bronchopleural fistula formation and extrapleural space infection[2,6,14,33,60,62,72,99,109].

The use of cavity drainage for the collapse cure of lung cavities had been attempted from time to time for many years before Monaldi[67] revived wide interest in its use in 1938. As advocated by Monaldi[67], the procedure consisted essentially of tube drainage and suction directly applied to the drainage tube. This procedure is likely to be complicated by hemorrhage from the chest wall and requires constant attention. As a result of these drawbacks the technique of cavernostomy evolved to simplify treatment. Cavernostomy consisted simply in the conversion to open drainage instead of the rather complicated tube drainage. This conversion to open drainage has largely supplanted in frequency the original tube drainage technique of Monaldi. The procedure has been used in tension cavities prior to the performance of thoracoplasty, and in so-called "blocked" cavities where the patient's condition contraindicates excisional surgery. It has been employed for drainage of cavities remaining uncollapsed after thoracoplasty. It also has possible indications in lower lobe cavities not amenable to thoracoplastic collapse and as a palliative procedure in far advanced cases. In evaluation of cavity drainage it may be said that indications for its use became progressively less. In the future, in all probability, the use of antibiotics will reduce the incidence of endobronchial disease with stenosis which is in a large measure responsible for the development of tension cavities for which the procedure is designed. With further antibiotic therapy and constant improvements in technique, more and more subjects will become better risks for resectional therapy rather than cavity drainage. It

is likely, however, that cavity drainage procedures will continue to have some use in the palliation of poor risk patients as a salvage procedure, although good long-term results under circumstances are not to be expected[3,54,71,81].

The original technique of extrapleural pneumothorax collapse was initiated by Tuffier[103] in 1893, who shortly after abandoned it after what was apparently insufficient time. However, the method was revived both by Schmidt[91] and by Graf[40] in 1937. Its subsequent use has established its main indication as limited to cases in which the pulmonary function is too doubtful to support thoracoplasty and in which there is extensive pleural space obliteration by adhesions. The procedure has also been employed in cases refractory to antibiotic therapy and bed rest where the lesion has pursued an acute fulminating course. The over-all mortality with the latter is high, 15%, but improvement is reported in 65%[20]. The commonest complicating factors in the use of the technique are delayed wound union, frank extrapleural space infection (31%) and space loss with consequent loss of collapse and reopening of lung cavity[20].

What has just been stated concerning extrapleural pneumothorax in the matter of indications for use and attendant complications may be reiterated for extrapleural pneumonolysis with paraffin plombage. The difference between the two procedures is that paraffin is placed in the extrapleural space rather than air to maintain the parenchymal collapse. The procedure was initiated and developed by Baer[6] but has never been widely popular for reasons already pointed out.

In 1946 Wilson[109,110] first advocated extrapleural pneumonolysis using lucite balls as the plombage material. The advantages cited are the lucite spheres cause little or no reaction in the tissue. The procedure has not gained wide usage due to the usual complications of infection of the space, dislocation of the plombage spheres and the danger of breakdown due to pressure necrosis. Although search for plombage material to obviate these drawbacks is under investigation, particularly regarding the employment of various synthetics including polyvinyl sponges and polyethylene sheeting, no ideal substance has been found.

The first use of supraperiosteal pneumonolysis and plombage was in 1928 by Lillenthal[60]. The indications for the procedure and the concept of the operation are the same as for the extrapleural operation. But in order to avoid necrosis of the cavity roof by pressure from the plombage material filling the space, the space is developed between the wholly denuded ribs and the periosteum and musculature. This allows the interposition of the additional thick layer of the periosteum and intercostal musculature between the plombage agent and the cavitated lung. As with extrapleural pneumonolysis, various plombage materials have been employed to maintain the collapse. Since then Wilson *et al.*[111] have employed and advocated the procedure in selected cases of the same type generally that are considered as indications for extrapleural pneumonolysis. Sequestration of the ribs at some time following the operation is a likely complication inherent in the process whatever plombage material is used, such as lucite spheres, polyethylene or other plastic substances. Should this occur, removal of the ribs is necessary. The procedure may if indicated, be supplemented with excisional therapy in the event that the lesions remain open or the sputum fails to convert within a reasonable time. At this time there is a dearth of clinical data on the long term results obtained by the procedure,

so that its value is difficult to assess. The indications are, however, that its widespread adoption is unlikely.

Beginning in 1937, Trimble and Wardrip[101], following a report by Vajda in 1933[106], became enthusiastic concerning the possibilities of introducing air into the peritoneum to perform parenchymal collapse. Intraperitoneal air of sufficient quantity will cause reduction of intrapleural volume by pressure elevation of the diaphragm and so produce collapse of the pulmonary parenchyma. This procedure, like the above, has been utilized as a compromise technique in effecting collapse where thoracoplasty or other forms have not been deemed feasible and has also been used as a supplement to them. It has been said to be efficacious, particularly in basilar cavitary lesions, not amenable to thoracoplasty and this is perhaps its most effective use. The technique of pneumoperitoneum has the advantage of being an easily induced reversible process which can be rather easily controlled and does not preclude or impair any subsequent form of definitive therapy. Aside from the rare danger of air embolism and the possibility of peritoneal infection there are few complicating hazards. On the other hand, the degree of collapse obtained by pneumoperitoneum is uncertain and inclined to be ineffectual in all but the most amenable cases. On this account, although it enjoyed some vogue, particularly in the late 1930's and early 1940's, its current employment is very rare in all but exceptional cases. At the present time these latter may possibly include cases in which chemotherapy is not tolerated; those in which the tubercle bacilli have become resistant, and those whose pulmonary function is so reduced as to be unable to tolerate more preferred forms of treatment. It may find additional indication as an aid to obliteration of pleural space and in expanding the lung after pneumothorax. It has been advocated in the control of pulmonary hemorrhage and as a form of collapse therapy for asthmatics and emphysematous subjects. Among the common contraindications to its use are instances of chronic fibrotic disease with thick-walled cavities, caseous areas with inspissated centers, endobronchial tuberculosis, peritonitis, tuberculous or nontuberculous, abdominal disease possibly or likely terminating in peritonitis, and umbilical or other abdominal herniae[17,22,104].

Reports of relatively large series of cases with late results are of value in judging the efficacy of the procedure. Trimble *et al.*[100] in 1948 analyzed 382 cases who had pneumoperitoneum longer than 3 months between 1935 and 1945 and following until 1946. Of these, 57% passed into the arrested phase of the disease, and 18% were definitely improved. However, it is to be noted that 15% of all patients had phrenic nerve paralysis in addition to pneumoperitoneum. The results of Mitchell's review in 1947[65] of 474 cases treated by pneumoperitoneum 3 months or longer are similar.

EXCISIONAL THERAPY. The present-day supersedence of excisional therapy in the treatment of pulmonary tuberculosis is actually the culmination of gradual advances in concept and technique made over a long period. These progressions at their inception had little or no relation to the application of excision techniques to the treatment of pulmonary tuberculosis. At first excision of protrusions of the lung were carried out incident to irreparable trauma, extensive infections, and new growth. It was not until considerable time had elapsed that surgical technique, anesthesia, and usage of antibacterial therapy had improved to a point that the specific application of excisional treat-

ment to pulmonary tuberculosis was feasible. Because its specific application to tuberculosis represents, in a sense, the culmination of a prolonged period of development, the evolution to the present-day period is briefly recalled. It is also to be borne in mind that the concepts of the role of excisional therapy in tuberculosis are by no means static and are continually changing. It is also likely that they will continue to do so. In any case this evolution of excisional therapy, past and current, is of universal interest for it illustrates the fact that concept and technique are mutually interrelated and limited by each other. Advances in technique extend the concept of their application and extensions of concept intensify the search for technical methods by which such concepts may be implemented.

The first recorded instance of excision of the pulmonary parenchyma was by Rolando of Parma in 1496[83]. The subject had received a stab wound of the chest through which the lung had herniated and become infected and gangrenous. This segment of the lung was excised by Rolando after 34 days with recovery of the subject.

Following Rolando's account there is an hiatus of almost three centuries until the further significant recording of successful pulmonary parenchymal excision.

In 1861, Jules Pean[76] excised what was apparently a tumor of the right chest at the level of the 4th interspace. This was carried out under general anesthesia and the visceral and parietal layers of the pleura sewn together before removing the growth. Hemostasis was accomplished by leaving the hemostats in place. The bronchi were not sutured because none were opened. The patient made an uneventful recovery.

It can readily be deduced from the above primordial accounts of excisional therapy that the procedures were fortuitously accomplished. Because there was little or no understanding of basic pulmonary function or structure, the subjects survived because of the inadvertent fusion of the visceral and parietal pleural layers by infection or tumor which allowed parenchyma of the lung to be removed with deflation of the lung by pneumothorax.

By 1880 the basic discoveries of anesthesia and antisepsis had been successfully exploited to the point that interest was greatly increased in the surgical possibilities of the chest. Unfortunately the marked success in abdominal procedures at this time was not extended to the thorax. Attempts at thoracotomy were promptly and disastrously likely to be attended by fatalities from respiratory failure. However, a broad international interest in the problem attending surgical invasion of the thorax had arisen and because of this, considerable animal experimentation was carried out between 1880 and 1900. Notable attempts to establish the causal disturbances incident to thoracotomy were made by Gluck in Germany[37], and by Murphy in the United States[69]. Perhaps the most important observation to be made during such experimentation was contributed by Murphy[69] (*vide supra*) concerning the relation of motion of the mediastinum to thoracotomy. Murphy showed that if the mediastinum were fixed the thoracic cavity could be entered with recovery of the animal subject. If, however, there were no fixation of the mediastinum, thoracotomy was inevitably attended by increasing respiratory failure and death. This significant fact was later to be re-emphasized by Graham[42] in his definitive studies on empyema in 1918. In the period of 1880 to 1900, lobectomy was infrequently attempted because of excessively high mortality and inevitable complications.

This was accomplished by crude mass ligation techniques so that the process was practically always attended by extensive slough, infection and fistulous communications between the pleural space and the lung.

Nonetheless, beginning with the quickening interest in the physiological principles involved in operations on the thorax, resections of the pulmonary parenchyma were more and more frequently attempted. These emphasized the importance of maintaining lung expansion during any intrathoracic procedure and numerous methods to accomplish this end were tried and reported along with results of various surgical procedures. Thus, in the period from 1890 to 1928, noteworthy reports are concerned with both anesthesia and technique. In 1891, Tuffier[102] resected the right apex of the lung for tuberculosis, employing an extrapleural method and closing the thorax without drainage. Ten years later, in 1901, Heidenhain[47] successfully accomplished a right lower lobectomy for bronchiectasis.

Appreciating the necessity for maintaining the expansion of the lung during thoracotomy, Sauerbruch[87] in 1904 attempted the use of a negative pressure chamber to accomplish this end. The difficulties were enormous but the chamber was employed, maintaining a negative pressure of 20 mm. Hg throughout the operation.

Following Sauerbruch's attempt, Meyer[63] in 1908, devised a positive pressure box apparatus which enveloped the head of the subject (as well as that of the anesthetist) to accomplish the same purpose which kept the lung expanded by the application of a positive pressure of 20 mm. Hg. The difficulty inherent in both the Sauerbruch and Meyer devices was, of course, the clumsiness of the apparatus and its difficulty in maintenance aside from the physical limitation to which it subjected the surgeon. However, the difficulties encountered with the maintenance of pulmonary inflation were shortly to be simply and definitively solved. This was first accomplished in 1909 when Elsberg[30] first employed endotracheal tube anesthesia which allowed the lung to be kept inflated with a negligible minimum of equipment which neither embarrassed the anesthetist or encumbered the surgeon. The efficacy and the ease of this technique were rapidly recognized and improved, largely by Magill[61] in the interval between 1900 and 1920, so that by the latter date endotracheal tube technique had become standard procedure in thoracotomy. Thus, in 1922 Lillenthal[59] was able to report 22 lobectomies performed under endotracheal anesthesia with a mortality of 42%. At about this period, 1923, Graham[42] reported successful lobectomies for bronchiectasis with the use of mass ligation of the hilar structures and the cautery. This practice lowered the mortality of removal of lung tissue and produced improvement in bronchiectatic patients by the elimination of diseased tissue. At this point, however, the anatomical approach to bronchial closure had not been envisaged and successful pneumonectomy had yet to be performed in human subjects.

Broadly viewed, the year 1929 begins the so-called present-day period in concept and practice of resectional therapy. In that year Brunn[12] reported 6 cases of one-stage lobectomy without one death. His technique consisted of clamping and doubly ligating the pedicle and after excision of the lobe, closure of the pedicle with a running chromic suture.

In 1932, Haight[44] reported 2 successful instances of two-stage pneumonectomy in which the pedicle was first ligated and the sloughed tissue subse-

quently removed. In this same year Shenstone and Janes[93] inaugurated the technique of tourniquet lobectomy. This was essentially a procedure in which the pedicle of the lobe to be excised was controlled by tourniquet while the individual structures of the pedicle were ligated with chromic suture. This considerably increased the safety of lobe removal and reduced the size of the residual stump. Because of these advantages the technique was generally accepted and widely employed until the experiences of World War II. The year 1933 was signal for two other advances: Graham and Singer[41] reported the performance of the first successful single stage total pneumonectomy for lung carcinoma. This definitely established the feasibility of the procedure and a new impetus was given to the application of resection procedures. Of equal import was Rienhoff's[82] contribution of introducing the method of individual structure ligation technique in total pneumonectomy. In this the individual vascular and bronchial structures of the pulmonary pedicle were separately ligated or closed. This permitted marked reduction in the size of the pedicle and a surety of closure with minimal slough. The advantages by these measures were so obvious that with but slight modifications they are currently in use.

Following these advances, Churchill and Belsey[18] in 1939, using the new established practice of individual ligation of vessels and bronchi, reported the successful resection of segments 4 and 5 (lingula) of the upper lobe of the left lung for bronchiectasis. This established beyond question that not only could the entire lung or its several lobes be successfully removed, but that even various segments of the lobes themselves could be removed under the proper technical management. Corroborating this concept, Kent and Blades[51] in 1942 presented a series of resectional cases in which lobectomy had been performed on a sound anatomical basis by the individual isolation and closure of the vascular and bronchial structures to the lobar parenchyma with subsequent minimal complications. This further established the necessity for precise technique in resectional procedures and at the same time proved that the complication of bronchopleural fistula need no longer be accepted as an inevitable complication of lobectomy or pneumonectomy.

With the advent of the World War II period, from 1942 to 1945, there was provided an intensely concentrated opportunity for the perfection of anesthetic and intrathoracic technique. The observation and treatment of large numbers of thoracic casualties advanced the knowledge and application of basic principles of respiratory physiology and evolved new concepts in the treatment of thoracic trauma. In this latter regard the use of pulmonary decortications in certain types of thoracic trauma is worthy of particular note. The work of Burford, Parker, and Samson[13], and Tuttle and others[105], established pulmonary decortication as a standard form of treatment in instances of organizing hemothorax and indicated that the procedure might also well be employed as a preferred form of treatment in nontraumatic cases of chest disease such as tuberculous and nontuberculous empyema. Thus the procedure of pulmonary decortication has come to assume a place in definitive treatment of tuberculous and nontuberculous chest lesions continuing to the present day.

The immediate post-war period of 1945 and 1946 was notable for intensive studies of the segmental anatomy of the lung and the formation of standard and acceptable nomenclature proposed by Jackson and Huber[49]. This interval

was also noteworthy as the beginning of an enormous amount of experimental and clinical use of the antibiotics applied to tuberculous and nontuberculous chest lesions. The increasing use and development of antibiotic agents, particularly in relation to the surgery of tuberculosis, dates approximately from this period.

In any case, the particular application of resection techniques and specifically segmental and subsegmental resection for tuberculous foci in lobes and parts of lobes was largely instituted by Overholt[75] in the interval of 1946 and 1947. This again was made possible by the advent of effective antibiotics and the detailed classification of the bronchopulmonary segmental anatomy begun in the immediate postwar period. Thus, effective antibiotic therapy in the stabilization of tuberculous lesions and accurate individual ligations made possible the considerable success attending segmental resections in tuberculous and other less prevalent affections such as bronchiectasis and the mycotic infections.

From this point onward, segmental resection was practiced with broadening indications and increasing frequency. By 1950 sufficient statistical and clinical evidence had accrued to indicate that resectional therapy might very possibly supplant or render obsolete most, if not all, of the hitherto chief forms of collapse therapy in pulmonary tuberculosis. From 1950 to the present day rapidly accruing clinical statistical evidence has supported this indication. Resectional therapy has at the present time supplanted many of the long established collapse methods previously employed. There is currently a widespread enthusiasm for its use. Prior to 1949, the time at which the introduction of streptomycin and paraaminosalicylic acid began to be widely employed, the high incidence of bronchopleural fistula and spread of the disease following resection acted as considerable deterents. However, with the application of streptomycin, paraaminosalicylic acid, and isonicotinic acid these complications have been largely reduced. Thus the scope of excisional therapy has continued to broaden. But again it must be emphasized that because of the relatively short time that excisional therapy has been practiced, long term results are not available so that enthusiasm for its use must be tempered with some caution until such are soundly established.

In any event it is appropriate at this time to evaluate the current status of resectional therapy in the treatment of tuberculosis. To make this evaluation it is perhaps necessary to reiterate certain generalizations implied in the foregoing.

In all instances of pulmonary tuberculosis a prolonged period of full physical rest and adequate antibiotic therapy is standard therapy to evaluate the nature of the lesion, stabilize the lesion, and improve the patient to optimum before possible definitive surgical treatment.

In all instances of the disease where definitive surgery is apparently indicated the selection of the surgical procedure to be carried out is based on the various features presented by the individual case. This selection is based on a decision between some form of collapse therapy, excisional therapy or a combination, usually staged, or of both. At the present time the most utilized form of collapse therapy is thoracoplasty, so that actually the choice in most cases lies between excisional surgery in the form of lobectomy, segmental, or subsegmental resection, or thoracoplasty.

It is very much at point, therefore, to examine the relative merits of excisional therapy in terms of contrast with

collapse treatment generally and thoracoplasty in particular.

Excisional therapy is the operative removal of diseased lung parenchyma. Thus, if all or the greater portion of a tuberculous lesion or focus can be excised there should be theoretically less danger of reactivation of the disease. This presents an immediate theoretical advantage over thoracoplasty or any other form of collapse treatment in which the lesion, usually cavitary, is collapsed but left *in situ*.

Generally speaking, excisional therapy has a far greater range of applicability than collapse therapy. Many of the well recognized typical lesions of tuberculosis are not amenable to collapse therapy. By this is meant that such lesions are little affected or benefited even when maximal collapse by thoracoplasty is obtained: for example, tuberculous bronchiectasis, tuberculomata, and thick-walled or tension cavities in unfavorable positions.

Again, excisional therapy may be applied to certain well localized lesions with a much greater conservation of pulmonary function than a similar or the same lesion subjected to collapse by thoracoplasty. This is true for the reason that excision of the diseased focus alone allows a much greater amount of functional parenchyma remaining, whereas to obtain adequate collapse by thoracoplasty considerable areas of parenchyma capable of function may have to be inactivated.

A not unimportant consideration is the relative deformity incident to excisional therapy and collapse by thoracoplasty. Both are to some extent deforming. But as indicated elsewhere, the deformity incident to thoracoplasty is at best very marked, while that incident to thoracotomy for excision is by comparison minimal.

Finally, excisional therapy presents the advantage of establishment of positive diagnosis by tissue study of any extant lesion. This is not possible by thoracoplastic collapse. There are instances when although presumed tuberculous, the lesion cannot absolutely be diagnosed as such, short of direct tissue examination which thoracotomy will permit.

By contrast it must be said that the operative mortality in excisional surgery may be higher than that attending collapse by thoracoplasty: that it can be positively stated as so is open to question. Undoubtedly there are cases which can withstand the usual staged thoracoplastic collapse which would poorly tolerate, if at all, thoracotomy and excision. Here again, as mentioned before, excisional therapy suffers doubt in evaluation because of a far smaller body of statistics concerned with the procedure.

In spite of a comparative lack of statistical data, particularly those concerned with long term results in excisional therapy, the indications for its employment have become progressively better defined since its inception.

The general requirements in any case where resection is contemplated are that the patient's general condition, particularly his cardiovascular status, be adequate to support the contemplated operation, and that the organisms present are still sensitive to the available antituberculosis antibiotic agents. More specifically, the following specific tuberculous lesions are generally conceded as indications for excision:

1) *The Round Discrete Focus.* These areas when tuberculous, may be formed by the walled-off residual of a caseous pneumonia, the coalescence of several discrete areas of caseous pneumonia, or by the inspissation with debris of a cavity whose bronchial communication is obstructed. They are classified as tuberculomata either mature or im-

mature, according to the stage of fibrosis or calcification, or both, present. In the immature form, the caseous center may contain live tubercle bacilli which may produce positive sputum in the patient if the lesion periodically evacuates into its communicating bronchus. In the mature forms, calcium appears concentrically or irregularly dispersed in the lesion, the tubercle bacilli contained are less liable to be viable and excavation to form cavity is unusual.

There is, however, in both immature and mature forms always the possible peril of cavitation and bronchogenic or hematogenous spread, or both. Further, neither conservative treatment nor any collapse technique including thoracoplasty will eliminate these lesions or insure against their possible breakdown. Hence, when a discrete round lesion can be positively identified as a tuberculoma, resection would seem to be definitely indicated. However, some competent observers feel that mature tuberculomata showing calcium deposition may be more conservatively viewed and that simple periodic roentgenograms to detect any progress in the lesion are sufficient.

A more rigorous policy of surgical excision is nevertheless favored in dealing with tuberculomata because of the generally good results that have attended excision to date.

Additional emphasis for excisional treatment lies in the fact that not all round discrete foci are tuberculomata. An unfortunately high percentage may be malignant and the malignancy may in rare instances be present in spite of obvious calcification.

2) *Cavitary Disease Not Amenable to Thoracoplastic Collapse.* Cavitary disease may be little affected by collapse by thoracoplasty because of any one, a combination of two, or all three common attendant conditions: their position in the pulmonary parenchyma, the character of the cavity wall, and the condition of "tension" brought about by entrapped air from a stenosed bronchial communication.

Anterior, apical, hilar, basilar, and paravertebrally located cavities simply by their position are extremely difficult to close by collapse therapy (for example, thoracoplasty). In these positions even extensive thoracoplastic procedures are likely to produce inadequate effect for closure.

The character of the cavity wall to a large extent determines its possibilities for thoracoplastic collapse. Thick fibrosis of the wall may render it wholly unamenable and unaffected, as may epithelialization to form a cyst-like lining. So-called "tension" cavities, produced by stenosis of bronchial communication to the cavity are the result of air trapped within the cavity caused by the valvular action of the stenosed bronchus, present a particular problem. In such the air is under positive pressure and may render collapse of any degree unlikely. Large or giant cavitary lesions, those which show periodic changes in size, particularly if they are thin-walled and show presence of fluid levels, are usually of the tension variety. The point to be made is that in all of the above cavitary types, excisional therapy is likely to be the preferred form of therapy rather than attempting thoracoplastic collapse.

3) *Bronchial Stenosis and Bronchiectasis Incident to Tuberculous Endobronchial Disease.* As a consequence of endobronchial tuberculosis, subsequent scar stenosis with bronchiectatic changes distal to the stenotic point may occur where well developed recurrent areas of atelectasis and infiltration appear in the lobes or segments accompanied by dyspnea and intermittent hemoptysis. Antibiotic therapy is usually extremely effective in controlling the infectious component associated

with this condition but can do little to the well advanced stenotic scar. Such cases are very little benefited by thoracoplastic collapse and excisional treatment of the affected lobes or segments is the obvious treatment of choice, provided that the subject's general condition and pulmonary reserve permit the procedure.

4) *Thoracoplasty Failures.* Whether from technically inadequate procedures, misjudgment in selection of cases, or unpredictable behavior of an individual lesion, a certain percentage of cases, which have had attempts at collapse therapy by thoracoplasty, must be classified as failures as evidenced by persistent cavity, sputum continuing positive, or progressive symptoms. Such cases may be alleviated by revision of the thoracoplasty in some instances, or cavernostomy may be selected because of reduced pulmonary reserve. But in practically all instances excisional therapy must be seriously considered as a likely treatment. In such instances it is particularly important to be certain that there is no unstable disease in the contralateral lung and that the pulmonary reserve is sufficient to support excision.

5) *Uncontrolled Exsanguinating Hemoptysis.* Under ordinary circumstances hemoptysis, even of considerable severity, can be readily controlled by immobilization of the effected side, adequate sedation and general supportive measures. On occasion, however, the episodes may be of such frequent and considerable amount as to endanger *immediately* the life of the subject from hemorrhage or actual drowning, or both, from the exuded blood. In such instances excisional therapy with ligation and removal of the localized area of the lesion may be the only measure, since collapse measures may already have been carried out ineffectually, or, if they have not, are likely to be inadequate for control.

6) *Differential Diagnosis in Suspected Malignancy.* As referred to above, the diagnosis between tuberculosis and malignancy may at times be extremely difficult. One or the other, rarely both, may be present and for obvious reasons a definitive diagnosis is mandatory. There are two general types of tuberculous lesions in which it is particularly difficult from roentgenograms and clinical findings to render certain distinctions from neoplasms. One is the discrete round focus or "coin" lesion already mentioned and the other is tuberculosis with atelectasis occurring in the high incidence of malignancy age group in whom the bronchoscopic and sputum studies are nonconclusive of either. In these instances excision with immediate biopsy is practically mandatory for positive differential diagnosis.

7) *Extensive Lung Destruction With or Without Empyema.* Extensive tuberculous damage to the lung as demonstrated by diffuse fibrosis, disseminated cavitation, extensive bronchiectatic changes, and stenotic sequelae is recognized as an indication for excisional therapy, particularly when associated with bronchopleural fistula or empyema, or both. Before carrying out the excisional procedure, usually pneumonectomy or pleuropneumonectomy, it is particularly important that the opposite lung be approximately normal or at least demonstrate no active disease. Pneumonectomy or pleuropneumonectomy[85] in which not only the affected lung but the infected pleural membrane are wholly excised is probably the most effective means of preventing bronchogenic spread and persisting infection from the chronically suppurating pleura. In these instances the affected lung is so damaged and its functional activity so reduced that the respiratory reserve of the subject is

little affected by total removal. Regardless of how definitely indications, such as the above, point to the advisability of resectional treatment, excisional removal of various portions of the lung parenchyma is carried out always with the possibility of several common complications.

The most common of these is wound infection. It is also usually the least serious. It is probably true that infection following thoracotomy is somewhat more frequent than in other types of electively performed procedures which on the whole have a very low occurrence rate. When incident to excisional therapy such wound infections may or may not be tuberculous. In either case the infection is usually readily controlled, although drainage, revision, or secondary closure may be required for eventual healing.

Dissemination of the disease following excisional surgery is always a possible hazard, although apparently progressively decreasing where an adequate pre- and post-operative antibiotic regimen has been observed. In this regard it may be mentioned that there is some opinion that the compensatory distention of the remaining lung predisposes to reactivation of quiescent disease foci that remain. Actually it is probable that many factors may be causal of postoperative disseminations: aspiration of infected exudates into uninvolved bronchi during anesthesia, opening of unstable foci during the procedure, the appearance of predisposing complications following operation such as empyema and bronchopleural fistula may all be primary or contributory.

Probably the most frequent endothoracic complications following excisional therapy are the more or less related sequelae of inadequate re-expansion of the residual lung, empyema, and bronchopleural fistula.

Ideally where a lobe or segment of affected lung parenchyma is excised, the space formerly occupied by the excised segment is filled by the increasingly distended residual lung segments. This compensatory emphysema and the adherence by adhesion of the visceral pleura to the chest wall eliminate space so that the volume of the pleural space is completely filled by the lung parenchyma, maintained in position by its distention and pleural adhesions. When for any reason the lung does not expand and adhere to the parietal pleura a space remains which represents the difference in volume between the pleural cavity and the contained residual lung tissue. The causes for such space formation due to lack of lung re-expansion may be single or multiple; bronchial obstruction from retained secretions may render the lung segments atelectatic, accumulation of exudates from poor drainage of the pleura may accumulate to compress the parenchyma. Fistulae may form between the bronchi and the pleura which allow ingress of bronchial air into the pleura and passage of any pleural exudates into the other ramifications of the pleurally communicating bronchus. The failure of re-expansion of the lung, space formation, empyema, and bronchopleural fistula are closely related and the presence of one predisposes to the incidence of the other. Any one or all of the above are particularly prone to occur in instances where excision has been performed in markedly debilitated subjects where the disease is extensive and much diseased tissue has been allowed to remain, and where undue injury to the remaining bronchopulmonary tissue has occurred during the excision.

In any case the elimination of persistent pleural space and the treatment of empyema or bronchopleural fistula, or both, constitute frequently recurring

problems in excisional therapy. It is in regard to this problem that thoracoplasty bears an intimate relationship to excisional therapy. In this respect, however, thoracoplasty is not employed as a collapse measure, but as a means of eliminating persistent pleural space or empyema, or both, or bronchopleural fistula, or any combination of these. Briefly stated, the underlying concept is that since persistent pleural space predisposes to, causes the formation of, and tends to perpetuate the existence of empyema and bronchopleural fistula, such persistent space must be eliminated. Thus, if the residual lung cannot be made to fill the space, the chest wall must be made to fill it by making the wall conform closely to the contour of the residual lung. Hence the term "tailoring thoracoplasty," the purpose of which is to "fit" the chest wall to the residual lung and thereby eliminate the persistent space with its predisposition to empyema or bronchopleural fistula, or both.

With the above considerations in mind, the relation of supplementary thoracoplastic and other procedures currently employed in conjunction with excisional therapy become more clarified. Thus thoracoplasty is always a possible necessity following excisional surgery. In general the greater the amount of lung tissue removed, the greater is the likelihood of larger persistent space, and the greater the extent of the tailoring thoracoplasty to eliminate it. As to just what circumstances necessitate thoracoplasty, the extent of the thoracoplasty, and when it is best performed, there is currently some difference of opinion. Thoracoplasty may be carried out previous to excisional surgery, at the same time, or following it. The relative merits of preoperative, concomitant and postoperative thoracoplasty, are no doubt to be judged in terms of their application to the individual case. In general, however, it may be said that concomitant thoracoplasty avoids multiple stage operations but prolongs operative time during the actual excisional surgery and increases the likelihood of shock. Preoperative thoracoplasty very probably will render the subsequent excisional therapy more difficult technically. In postoperative thoracoplasty adhesions incident to the excisional surgery may keep the residual lung distended in spite of extensive thoracoplasty.

Another procedure aside from that of tailoring thoracoplasty is frequently employed in the treatment of the related complications of resectional surgery: residual space, empyema, bronchopleural fistula. This is pulmonary decortication. While thoracoplasty is designed to eliminate space by "tailoring" the chest wall, decortication is utilized to abolish such space by increasing expansion of the affected lung, thereby tending to obliterate empyema and close the bronchopleural fistula if present. The background of the development of the use of pulmonary decortication in tuberculosis is of some interest. The first recorded instance of its use was by Delorme[27] in 1894. Delorme's procedure bears little resemblance to the technique of decortication currently employed. In Delorme's original case a portion of the lung was found encased in a restricting fibrous covering which he incised by multiple cross-hatched incisions. He did not remove the fibrous covering overlying the parenchyma but the release of the covering by incisions through its substance allowed release and re-expansion of the underlying lung. At that time Delorme's report attracted little attention and the possibilities of its wider application were generally ignored. It was not until World War II with its large number of surviving chest injuries that pulmonary decorti-

cation again came into prominence and ultimately became established as an effective form of treatment. This was primarily due to the rediscovery of the procedure by Burford in 1943, closely followed by others as previously noted, who had primarily applied the technique to instances of clotted hemothorax incident to war injuries. The actual procedure employed bore little resemblance to that originally outlined by Delorme, for in the latter day, the organizing fibrous covering of the lung was actually stripped and removed from the underlying parenchyma. So successful was its use in dealing with instances of traumatic hemothorax in which there existed coincident empyema, and bronchopleural fistula in the period of 1943 to 1945, that it was subsequently applied to other rarer conditions in which the same features obtained, namely in tuberculosis where residual pleural space, bronchopleural fistula and empyema were complicating factors, primarily or as a result of excisional therapy. At the present time it is employed with excellent results in selected cases of noninfected and infected organizing hemothorax, acute and chronic nontuberculous empyema, and "trapped" or "captive" lung incident to pneumothorax. It is also employed, as noted above in conjunction with excisional therapy and thoracoplasty to obtain obliteration of residual cavity. Not infrequently there are instances in which the decortication is utilized to obtain further expansion of the lung residual following excision and is itself followed by thoracoplasty to obliterate any remaining pleural space. In all such instances the use of decortication is based on the primary rationale of eliminating pleural space by improving or increasing the expansion of the lung underlying a restrictive fibrous covering.

When in a small percentage of instances residual space, empyema, and bronchopleural fistula remain despite decortication or thoracoplasty, or both, still other means must be taken for their elimination[3]. These consist in so-called "deroofing" operations in which the entire space or involved area is opened widely to its boundaries by removing the overlying segment of the chest wall so that the entire space is patent. This eliminates any problem of adequate drainage and permits the subsequent coverage of the residual space, empyema, or fistulous area, with skin grafts or muscle overlay. Fortunately the instances in which this ultimate procedure is necessary are very infrequent for it is essentially and unavoidably mutilating[3].

Evaluation of any basic form of treatment rests eventually upon the results obtained in a large number of cases and over a significant period of time. For this reason, as emphasized elsewhere, a fully accurate estimate of the role of excisional therapy in the treatment of pulmonary tuberculosis is not yet possible. This is evident for the reason that the practice of excisional therapy in tuberculosis is relatively recent. Nevertheless the results as reflected by the related general statistics have been most encouraging and continue to be so. In association with these statistics it must be borne in mind that the widespread practice of excisional therapy actually has existed only about a decade. In that time the mortality for pneumonectomy has fallen from 25% to 10%, that of lobectomy from about 17% to 2%, and that of segmental resection from the region of 10% to 3%[107].

Aside from the operative mortality concerned, the incidence of complications attending various resectional procedures has also fallen markedly. The incidence of spread of disease incident to operation has been reported as only

between 2 and 3%[107]. Empyema and bronchopleural fistula incident to lobectomy in tuberculosis has been recorded as low as 2%, and these complications following segmental resections at even lower figures. Further, the statistics for beneficial results obtained, although only covering short periods, would seem to warrant continuing cautious optimism.

A recent series of 53 patients with postoperative follow-up of from 15 to 27 months, reports a sputum conversion rate of 90%[84]. Another reporting 80 cases followed for 36 months records a sputum conversion of 84%[35]. One hundred patients in still another series, some of which received no antibiotic (streptomycin) and were followed for 4 years, showed an 87% conversion rate in those surviving[7]. Of those surviving who subsequently received antibiotic treatment in an additional 100 patients, the conversion rate was 91.5%. Another large series of 202 resections followed from 6 months to 5 years records a sputum conversion rate of 85%[24].

It is apparent that various factors have entered into the present day concepts of the treatment of pulmonary tuberculosis in general and the relationship of excisional therapy to management of the disease in particular. Of these factors certainly one, if not the outstanding of those responsible, is the advent and adoption of antibiotic treatment of the disease. Because of its unquestioned importance in this regard it deserves at least comprehensive comment.

Following in the wake of the wide interest aroused by the clinical successes of the sulfonamides and penicillin, an intense search was made for any similar antibiotic agent possessing effective properties against the tubercle bacillus. This search was rewarded by the discovery of streptomycin by Waksman[90] in 1944 and reported as definitely valuable against the organism by Hinshaw and Feldman in 1945[48]. Its efficacy was immediately confirmed and by 1946 was made sufficiently available to carry on full scale treatment in a significant number of cases. In spite of a considerable body of investigations at that time and carried on consistently to the present, the mode of action of streptomycin against the tubercle bacillus is unknown. From its *in vitro* and *in vivo* behavior in this respect the drug is presumed to be bacteriostatic rather than bactericidal. Its greatest effectiveness is in massive pneumonic infections of the exudative type, in diffuse caseous lesions, recurrent disseminations, and particularly in stabilizing the disease before and following definitive surgical procedures concerned with excisional or collapse therapy. The drug has little or no demonstrable effect in long-standing fibrotic or productive residua. Unfortunately it was early established in observations on the clinical effect of the drug and amply confirmed thereafter, that the tubercle bacillus is likely to establish such resistance to it as to render it comparatively ineffectual when the drug alone is employed. This is also particularly liable to occur in instances when streptomycin is used in comparatively large doses and over protracted periods. In fact, it may be generally said that the development of streptomycin resistance increases directly with the amount of the drug and the length of time it is administered. The appearance of this resistance is of such consequence for obvious reasons that some standard criterion of its occurrence is essential. Thus, at present a positive state of resistance has been defined as any detectable growth of the tubercle bacillus on specific culture media containing a concentration of 10 micrograms of an established standard preparation of the drug. The relative

resistance is estimated by the number of colonies appearing on the streptomycin-impregnated medium with these growing on a control culture without streptomycin[98].

The time of onset of streptomycin resistance cannot be sharply defined, but in general the likelihood of its appearance when the drug is used alone greatly increases after the sixth week of administration[17,104].

Fortunately the hazard of the appearance of this resistance factor to streptomycin can be greatly reduced by giving the drug in combination with para-aminosalicylic acid (PAS). The use of this agent began in 1949, and, after full clinical trial, was found to possess some bacteriostatic action on the tubercle bacillus. Its main action and greatest efficacy, however, is in the prevention of the onset of streptomycin resistance by the organism. Just how para-aminosalicylic acid creates this important effect is not known, although considerable investigation has been undertaken to determine it. Other antibiotic agents, for example terramycin, possess the same effect and exert the protractive action to a lesser degree. These latter may be used in combination with streptomycin when the subject cannot tolerate PAS[98].

The continuing search for more effective antibiotic agents[9,43,94] resulted in the trial of isonicotinic acid hydrazide (INAH) in 1952. Since that date this agent has been in active clinical use. This agent has been shown to have about the same or slightly greater potency than streptomycin in arresting action on the tubercle bacillus. It apparently permeates tissues more readily than streptomycin and has the additional advantage that it may be taken orally. As with streptomycin, organism resistance to isonicotinic acid hydrazide is prone to develop rapidly if the drug is taken alone, definite resistance showing from 4 to 6 weeks. This resistance phenomenon can be obviated by giving the drug in combination with either streptomycin or PAS[98].

The development of surgical therapy for pulmonary tuberculosis is well established. The progress which has been made in the development of a surgical approach has resulted in lessening of the need for expansion of the facilities for sanatorial care. Long term beds for care of the tuberculous patient are obviously necessary even with surgery, but in any instance the length of the stay in the sanatorium is markedly lessened. The additional advantages offered by the use of antibiotics gives added hope that in the near future the high toll of disability and death from pulmonary tuberculosis will be rapidly brought under reasonable control[17,22,104].

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OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.
AND
HENRY P. WAGENER, M.D.
ROCHESTER, MINNESOTA

LESIONS OF THE OPTIC NERVE IN EXOPHTHALMOS OF ENDOCRINE ORIGIN

BY HENRY P. WAGENER, M.D.
ROCHESTER, MINNESOTA

As stated by Cordes[10], there is a disturbance in the balance between the thyroid hormone and the thyrotropic hormone of the pituitary in most cases of exophthalmos of endocrine origin. Falconer and Alexander[21], for instance, found excessive amounts of pituitary thyrotropic hormone in the blood of 8 of 11 patients with malignant exophthalmos. However, the occurrence of cases such as that reported by Medine[45] in which no such disturbance can be demonstrated, suggests that an exophthalmos producing substance may be distinct from the thyroid-stimulating hormone. According to Medine[45], Jeffries[35] obtained in experimental animals highly suggestive evidence of the existence of two separate factors, one being responsible for the exophthalmos and the other exerting a stimulating action on the thyroid gland. Smelser and Ozanics[59] stated that the power of pituitary extracts to produce exophthalmos is not necessarily proportional to their content of thyrotropic hormone but that the exophthalmos producing factor is much more closely associated with the thyrotropic hormone than with any other single principle, including corticotropin and the growth hormone.

Dobyns and Steelman[17] stated:

> "The experimental evidence which has been presented indicates that when anterior pituitary extracts are administered to animals, TSH *per se* is not responsible for the development of exophthalmos. It appears that there is another substance which produces the exophthalmos. We have proposed to call this exophthalmos producing substance (EPS). . . .
>
> "The failure to show a high titre of TSH in all patients suffering from progressive exophthalmos has perhaps been more frequently attributed to the inadequacy of the assay methods than to the possibility that TSH might not be responsible for the problem concerning the eyes. As a result of the findings described here, an assay method for the exophthalmos producing substance in selected clinical subjects is now being explored."

Later Dobyns and Wilson[18] stated that they had been able to demonstrate a substance capable of producing exophthalmos in minnows in the serum of some patients suffering from severe or progressive exophthalmos.

In the majority of patients with thyrotoxicosis, exophthalmos, if present, is not materially progressive. In a relatively few instances, however, steadily progressive exophthalmos develops. In the words of Hedges and Scheie[32], "It is not widely recognized that exophthalmos associated with thyroid disease can be accompanied by visual loss

due to involvement of the optic nerve." Excepting the reports of Brown and Schwartz[9] and of Goldzieher and associates[30], the latter of which is difficult to classify, lesions of the optic nerves are said to occur only in cases of the progressive type of exophthalmos (malignant exophthalmos, exophthalmic ophthalmoplegia). Dobyns[16] stated that severe progressive exophthalmos may develop in the course of Graves's disease with thyrotoxicosis, after thyroidectomy when the picture of thyrotoxicosis has been ameliorated or in individuals without goiter or thyrotoxicosis. Millikan and Haines[47] studied 21 patients with exophthalmic ophthalmoplegia. They found that, at the time the ophthalmoplegia developed, nine of the patients were hyperthyroid, seven were euthyroid following thyroidectomy and five showed no evidence of past or present thyrotoxicosis. Mann[42] expressed the opinion that malignant exophthalmos is not a separate disease entity but only the extreme stage of the exophthalmos associated with thyroid disease. She observed malignant exophthalmos in 3 patients presenting primary thyroxine deficiency with compensatory excess of thyrotropic hormone, in 9 patients whose histories suggested antecedent excess of thyroxine followed by spontaneous thyroid failure or thyroidectomy and subsequent excess of thyrotropic hormone, and in 7 patients in whom excess of thyroxine and excess of thyrotropic hormone developed simultaneously. It would seem that the local tissue changes in the orbit would be the only factor common to all these disease states which might affect the optic nerve.

PATHOLOGIC CHANGES IN THE ORBIT IN PROGRESSIVE EXOPHTHALMOS. Martens[43] stated that in the orbits in cases of exophthalmic goiter of the usual type Mulvany[48] found widespread neuromuscular degeneration, occasional infiltration of round cells, fat infiltration, and some fibrous replacement in the disintegrating muscle and nerve cells. Mulvany[48] contrasted these findings with those in the orbits in cases of malignant exophthalmos, enlargement of the muscles, fibrosis which is often widespread through the muscles, edema, degeneration and round cell infiltration. Martens[43] commented, in agreement with Mann[41], that the changes described could represent an early and a late phase of the same pathologic process. According to Cordes[10], Bedrossian[3] stated that in the exophthalmos of thyrotoxicosis there is general wasting of muscle fibers with loss of striation, fibrillation and amorphous granulation of the sarcoplasm; the muscles are normal in size; there is no edema or infiltration of round cells, but there is an increase in the amount of muscle and orbital fat. Dayton[14] stated that Rundles and Pochin[56] studied the orbital contents removed at necropsy in 17 cases of Graves's disease; they found an increase of orbital fat and infiltration of the extra-ocular muscles with fat. In so-called thyrotoxic exophthalmos, according to Duke-Elder[19], the pathologic changes in the orbit are not marked but include edema, an accumulation of fat particularly infiltrating the muscles, and a degeneration of the muscles without dense infiltration or fibrosis.

Cordes[10] stated that in the orbits in cases of progressive exophthalmos Bedrossian[3] found the muscles much larger than normal, with interstitial fibrosis, edema and chronic inflammatory lymphocytic infiltration; that Gleason[29] reported idiopathic myositis with muscles eight times the normal size; and that Cordes had found the muscles to be markedly enlarged. Dayton[14] noted that Terplan and his co-workers[63] had found, at necropsy of

a patient with far-advanced exophthalmos, generalized myositis which was most marked in the muscles of the heart and in the extra-ocular muscles; there was an inflammatory infiltration with many eosinophils, lymphocytes and macrophages. In their cases of progressive exophthalmos, Falconer and Alexander[21] described edema of the interstitial tissue of the muscles, often associated with degenerative changes in the muscle fibers, and accompanied by lymphocytic infiltration and later by increase in fibrous tissue. Dobyns[16] reported the results of microscopic studies of orbital tissues from 5 patients who had undergone enucleation because of malignant exophthalmos. He described characteristic infiltration of orbital fat and muscles with edema, lymphocytes and macrophages, young and old forms of connective tissue and phagocytosis of fat in large tissue macrophages; fat was deposited in the muscle fibers in one case.

Dobyns[16] noted that the retrobulbar tissue is under pressure, due apparently to increase in volume. This increase in intra-orbital tension seems to be one of the most characteristic distinguishing features of progressive exophthalmos. Thus Cordes[10] stated that in cases of nonprogressive exophthalmos there is no evidence of increased retrobulbar pressure and it is possible to push the globe back into the orbit by firm, gentle pressure. In cases of progressive exophthalmos, by contrast, definite retrobulbar resistance prevents the globe from being pushed back into the orbit. In Naffziger's opinion[50], this increased pressure in the orbit is more significant than the degree of exophthalmos, and he implied that the intra-orbital tension may be equally high, with exophthalmometer readings of 24 and 36 mm. The resistance to backward pressure of the globe into the orbit can be measured accurately by orbitonometry, and the course of its increase in cases of progressive exophthalmos can be followed, as noted by Means and Stanbury[44] and by Danis and Mahaux[12].

According to Fralick[24], Asboe-Hansen and Iversen[1] demonstrated accumulations of mast cells and hyaluronidase-sensitive mucopolysaccharides in the connective tissue at various sites in guinea pigs treated with thyrotropin. These changes were most prominent in the retrobulbar tissues. The authors postulated that, since mucopolysaccharides, particularly hyaluronic acid, are known to possess a striking capacity to bind water, an increased content of these substances in the orbit might explain the protrusion of the eyes. Duke-Elder[19] stated that, in advanced cases of exophthalmic ophthalmoplegia, the muscles appear pale, become cartilaginous in texture and are sometimes enormously enlarged to six or seven times their normal bulk. Histologic examination of the muscles shows, instead of infiltration with fat, interfascicular edema with patchy infiltration of lymphocytes and diffuse fibrosis. The enormous increase of the orbital contents, essentially of newformed fibrotic tissue, provides the only acceptable explanation of the extreme and irreducible exophthalmos. In biopsy specimens of extra-ocular muscles taken at the time of orbital decompression, Naffziger[50] found gross swelling with edema, loss of striation and varying degrees of cellular infiltration up to enormous lymphorrhages; marked fibrosis was present in some muscles and occasionally hyaline changes. Orbital fat was notable by its absence; it was always less than normal in amount.

Rundle, Finlay-Jones and Noad[55] made a quantitative analysis of the orbital tissues removed at necropsy in a case of malignant exophthalmos. A man who had had progressive exophthalmos

for 5 months died as the result of a coronary occlusion. The globes had been turned downward and inward with only the medial recti functioning. Congested edematous conjunctiva had protruded through the palpebral fissures, and both upper lids had bulged considerably. There had been firm resistance to light pressure on the globes. The scleral veins had been engorged and prominent, and the retinal veins had been engorged. The visual fields had been normal. Control material was obtained from male subjects without exophthalmos and from 3 males who had had thyrotoxicosis with exophthalmos. The bulk of the orbital tissue was greater than that in the normal and thyrotoxic controls. The excess bulk of the orbital tissues was due solely to enlargement of the orbital muscles, which were approximately four times the size of those in the normals and three times the size of those in the severely exophthalmic thyrotoxics. The residue, the fibrofatty tissue of the orbit, was normal in weight, the water content was raised but the fat content was lowered as compared with normals. The water and dry fat-free components of the orbital muscles were increased by some 400%; 98.6% of the increase of bulk was in the fat-free components. (In the thyrotoxics, the muscle bulk was increased by only 25% and fat accounted for more than half the increase.) Histologic examination showed that the muscle fibers were enlarged and degenerated but not increased in number, that there was much increase in the connective tissue elements and that there was some infiltration with lymphocytes and plasma cells. The authors concluded that the critical factor in exophthalmos is the ratio between orbital tissue bulk and orbital volume. The association of bulged lids, epiphora and chemosis has led to the erroneous assumption of widespread orbital edema. However, edema of the orbital contents may be a terminal development when extreme degrees of overfilling cause obstruction of the orbital veins.

TYPES OF OPTIC NERVE LESIONS. Duke-Elder[19] stated that the vision remains unimpaired in cases of exophthalmic ophthalmoplegia unless complications develop. Unfortunately, these are frequent and include exposure keratitis, which may terminate in endophthalmitis and loss of the eye, and papilledema resulting in optic atrophy, "a tragedy which tends to occur in the very recalcitrant cases following thyroidectomy." Retrobulbar neuritis is a rare complication.

Walsh[65] stated that it has been generally believed that there are no ophthalmoscopically visible changes in hyperthyroidism and that this is true generally speaking, although Brown and Schwartz[9] among others have recorded optic neuritis. He noted that Fournier and Helquera[23] observed bilateral optic neuritis with pronounced loss of visual acuity in a case of myxedema and collected from the literature a case of bilateral retrobulbar neuritis with central scotomas and 3 cases of bitemporal hemianopsia. Walsh[65] suggested that these may have been cases of acromegaly with secondary hypothyroidism and said that "the evidence is that myxedema alone never, or only extremely rarely, accounts for changes either in the optic nerves or in the visual fields." With reference to progressive exophthalmos, Walsh[65] said: "The visual acuity is reduced as a result of corneal edema and clouding of the cornea. Within the eyes there is likely to be papilledema, hemorrhages and exudates. In one instance I have observed horizontal ridges in the retina as described in tumor of the orbit." A similar observation was made by Mann[42] in a case in which

progressive exophthalmos developed 6 weeks after thyroidectomy. Vision was reduced to ability to see hand movements by edema and tension lines in the retina resulting from pressure of the tense orbital tissues on the globe. Edema and folds in the retina were described by Steinmetz[62]. Also Cordes[10] observed folds in the retina around the optic nerve in one of his cases; partial optic atrophy with some loss of vision developed later.

In her discussion of pituitary exophthalmos, Hermann[33] stated:

> "Visual defect as met with in this syndrome may be due to a variety of lesions: to swelling or ulceration of the cornea, to partial detachment of the retina . . ., to severe stretch of the optic nerve . . . or to long-standing papilloedema with subsequent optic atrophy. This last possibility is rather theoretical; if orbital edema which is sufficiently severe to cause papilloedema remains unrelieved, the eye will be lost before optic atrophy has developed."

Naffziger[50] noted that visual loss appears in the late stages of progressive exophthalmos and may be due to a variety of causes. Drying of the cornea may cause blurring, but the more serious losses are due to corneal ulceration, choked disks, and changes in the visual fields, which may vary from slight peripheral constriction and enlargement of the blind spot to marked irregular loss of field. Reduction of visual acuity caused by choked disks with retinal hemorrhages occurred in 17.5% of his cases and blurring of the disks was present in a larger number. Spaeth[61] called attention to the fact that the so-called papilledema is not due to increased intracranial pressure. In his opinion, it is actually an edema of the retina proper. Edema of the peripapillary retina advanced to such a stage in two of his cases that a true retinal separation occurred, with degeneration of the retina and an enormous stationary blind spot. Lyle[40] observed in 2 cases pallor of the optic disks, which he ascribed to ischemia of the optic nerves.

Poppen[53] stated that scotomas of various sizes may be present in various parts of the visual fields of patients in whom exophthalmos is associated with considerable retro-orbital resistance. Scotomas may involve only quadrants or the entire lower or upper half of the visual field. The scotomas may become sufficiently large to cause virtual blindness. Cordes[10] also noted that nonspecific field changes and marked diminution of visual acuity may occur in the more severe cases of progressive exophthalmos. In one of his own cases, the field of the left eye was only mildly generally constricted, but that of the right eye was reduced to a residual upper crescent of vision.

PROGRESSIVE EXOPHTHALMOS AND GLAUCOMA. Walsh[65] made the interesting observation that the intra-ocular tension was increased in several of his cases, owing to the increased intra-orbital pressure. Givner, Bruger and Lowenstein[28] noted a rise of intra-ocular tension to between 35 and 40 mm. Hg (Schiøtz) in 2 patients with marked widening of the palpebral fissures due to contraction of Müller's muscle in the upper lid. They thought that this rise in tension, which was not accompanied by any visual field defect, was caused by mechanical pressure of the upper lid on the globe and was not a true glaucoma. Beierwaltes[4] stated that glaucoma is sometimes associated with malignant exophthalmos and that it is usually improved by control of the exophthalmos. Keyes and Parisi[38] reported a case of malignant exophthalmos of undetermined origin (questionably thyrotoxic) in which edema of the orbits, eyelids and conjunctiva was associated with severe glaucoma. The right eye became blind, and the vision of the left eye

was reduced to 20/200 as a result of the glaucoma. Juler[37] also described a case of severe exophthalmos with chemosis, which was complicated by glaucoma.

In discussing the diagnosis of pituitary exophthalmos, Braley[8] said:

> "I believe one of the most consistent findings is demonstrated by the tonometer. When the intra-ocular pressure is measured in the resting position of the eyes, the pressure may be high normal or moderately elevated (25 to 35 mm. Hg [Schiøtz]). This resting position is frequently from 5 to 10 degrees below the perpendicular. When the pressure is measured in the semireclining position and the eyes looking upward 10 to 15 degrees above the perpendicular, the tonometer readings increase 10 to 30 mm. Hg."

Braley reported such a case, in which the intra-ocular pressure measured 80 mm. Hg (Schiøtz) in one eye and 60 mm. Hg in the other eye in the primary position. When the pressure was measured in slight downward gaze, it was reduced to 60 and 40 mm. Hg respectively. Papilledema was present and the vision was reduced to 6/30 and 6/15. The exophthalmos measured 29 mm. in each eye. The patient was euthyroid. On desiccated thyroid therapy, the exophthalmos decreased in 2 months to 24 mm. in each eye, and the intra-ocular pressure fell to 19 mm. Hg in each eye. The papilledema disappeared and the vision returned to normal. Papilledema and acute glaucoma were present in a case of hyperthyroidism with exophthalmos described by Friedenwald[25].

EDEMA OF THE DISK IN PROGRESSIVE EXOPHTHALMOS. In addition to the cases previously mentioned, edema of the disks was noted in 6 cases collected from the literature by Danis and Bastenie[11], in 2 cases each reported by Thomas[64] and by Lyle[40], and in single cases reported by Engel[20], Jones[36], Hedges and Scheie[32], Gedda and Lindgren[27], Falconer and Alexander[21], Schneider and Gardner[57], Dayton[14], and Paufique and associates[52]. Offret and Offret[51] stated that choked disks may or may not be accompanied by loss of vision. However, the vision was definitely reduced in 16 of these 18 cases; the vision was not recorded in 2 cases. Offret and Offret[51] remarked also that it is questionable whether the edema of the disk is caused by compression of the optic nerve by orbital edema, whether it indicates increased intracranial pressure, or whether it represents optic neuritis. Various diagnoses were made by the observers in the 18 cases discussed here. The diagnosis of papillitis was made in the 6 cases recorded by Danis and Bastenie[11], of retrobulbar neuritis in Engel's[20] case, and of optic neuritis in one of the cases reported by Thomas[64]. Choked disk was the diagnosis in the case of Schneider and Gardner[57] and papilledema in 6 cases (Jones[36], Gedda and Lindgren[27], Falconer and Alexander[21], Thomas[64], Dayton[14], Paufique and associates[52]). Hedges and Scheie[32] and Lyle[40] recorded simply edema of the disks in their cases.

Offret and Offret[51] noted that the late results of the optic nerve involvements are not always good. If the intra-orbital hypertension is relieved in time, the outcome is usually favorable; but there are cases which terminate in optic atrophy. Normal vision was regained apparently in Thomas'[64] 2 cases, in the cases of Engel[20] and of Falconer and Alexander[21] and in one eye in the cases reported by Gedda and Lindgren[27] and by Hedges and Scheie[32]. Partial optic atrophy was noted in one eye of Hedges and Scheie's[32] patient, and residual scotomas were noted in both eyes of one of Lyle's[40] patients and in one eye of Gedda and Lindgren's[27] patient. The final vision was 6/15 or less in 4 of the 6 cases recorded by Danis and Bastenie[11], and there

was no improvement in vision in the case reported by Jones[36]. The final vision was not stated in Schneider and Gardner's[37] case and in one of Lyle's[40] cases.

LOSS OF VISION WITH NORMAL OPTIC DISKS. Offret and Offret[51] stated that, in their personal experience, retrobulbar neuritis, characterized by progressive failure of vision with central scotoma and without fundus lesion, was the most frequent type of optic nerve involvement in cases of malignant exophthalmos. Danis and Bastenie[11] collected reports of 13 cases with retrobulbar neuritis from the literature. Normal vision was regained in 9 of these; vision was reduced to 6/15 or less after an adequate follow-up in only 2 cases. It would appear, then, that the prognosis for recovery of vision is better in cases without ophthalmoscopically visible changes in the optic disks than in cases with such changes. Vision returned to normal in the case diagnosed as retrobulbar neuritis by Danis and Bastenie[12] but not in the case reported by Paufique and associates[52]. Normal vision was regained also in cases reported by Thomas[64] and by Hermann[33]. In the former, vision of the right eye had been reduced to ability to count fingers at 3 inches; in the latter, the vision of the right eye was reduced to 6/60 by a central scotoma in the presence of an ophthalmoscopically normal optic disk.

Igersheimer[34] described the visual changes present in 6 patients with progressive exophthalmos. One patient had a central scotoma in both eyes, two had a central scotoma in one eye and a temporal scotoma in the other, two had a central scotoma in one eye only, and one had no definite scotoma but had metamorphopsia in the lower field of one eye. The fundi were normal in five of the cases and showed pallor of the disks in the sixth. Four of the patients recovered normal or practically normal vision. One patient had only moderate improvement in vision after 1 month's treatment with thyroid and corticotropin. The sixth patient recovered practically normal vision in the left eye but at the end of 21 months was still only able to count fingers with the right eye because of the persistence of a central scotoma. This patient had thyrotoxicosis and was treated with propylthiouracil; the right optic disk was pale when treatment was started.

Hedges and Rose[31] reported their clinical observations in 19 cases of hyperophthalmopathic Graves's disease. Seven of the 19 had some loss of visual acuity. The visual impairment was due to corneal involvement in 3 cases, to the presence of scotomas in the visual field in 2 cases and was unexplained in 2 cases. Papilledema developed subsequently in the right eye of one of the patients with bilateral central and inferior altitudinal scotomas. None of the patients had permanent loss of vision attributable to the ophthalmopathy.

In 6 cases of exophthalmos associated with thyroid disease, Hedges and Scheie[32] were able to demonstrate defects in the central visual fields indicative of involvement of the optic nerve similar to optic or retrobulbar neuritis. One of these has already been discussed in the section on edema of the disk. The fundi were normal in the other 5 cases. Bilateral central scotomas were present in one case, unilateral central scotomas in 2 cases, a unilateral nerve fiber bundle type defect in one case, and a central scotoma in one eye and a nerve fiber bundle type defect in the other eye in one case. The vision and fields of all the involved eyes eventually returned to normal. All of the patients in this group had had hyperthyroidism at some time. At the time the field defects developed, two were moderately thyrotoxic, two were

mildly toxic or in remission, and two were euthyroid. The 2 patients who were moderately hyperthyroid had developed blurred vision and visual field defects within a few weeks after the onset of the metabolic disease. The vision and fields returned to normal in approximately 2 months, before control of the hyperthyroidism in one case. There seemed to be no correlation between the thyroid dysfunction and the eye lesions in the other patients. The degree of exophthalmos varied; the greater visual loss was not always on the side of the greater exophthalmos.

Hedges and Scheie[32] thought it possible that thyrotoxicosis did play some part in the production of the optic nerve defects in the first 2 cases. The predominant feature in these cases was the occurrence of central scotomas indicative of involvement of the maculopapillar bundle. A mechanical etiology was most likely in the other cases. The authors thought that a neurotoxic mechanism is possible when thyrotoxicosis is related to the onset or remission of the optic nerve defect and preferably when the exophthalmos is not outstanding. Danis and Bastenie[12] also thought that an excess of thyroid secretion might cause a lesion of the optic nerve in the sense of a toxic or inflammatory neuritis, though admitting that the visual disturbances develop more or less parallel with the changes in the orbital tissues.

The lesions of the optic nerves in cases of malignant exophthalmos are poorly understood, in Offret and Offret's[51] opinion. They noted that reports of histologic studies of the optic nerve in cases with visual failure are very rare. Merrill and Oaks[46] described the histologic changes in the orbital tissues, including the optic nerves, removed at necropsy from a man who had had post-thyroidectomy progressive exophthalmos for 2½ years. The orbital muscles, fat, nerves and vessels were bound together more firmly than normal by fibrofatty connective tissue. Microscopic examination showed marked atrophy of the muscles and optic nerve with fibrous and fatty areolar connective tissue replacement. Offret and Offret[51] commented that it is known that compression of the trunk of the optic nerve can cause foci of segmental degeneration with destruction of myelin and disappearance of the axis cylinders. This degeneration can be localized and can involve the macular bundle only. But in some cases, as in one of theirs after orbital decompression, the vision improves; so degeneration cannot have been the cause of the initial loss of vision. The question arises whether simple compression or edema may be the primary cause of the loss of vision. Danis and Bastenie[12] agreed that compression of the optic nerve can cause foci of degeneration in the nerve, but they thought that functinal recovery may be complete if the compression is removed soon enough.

THE MECHANISM OF THE OPTIC NERVE LESIONS. It would seem logical to assume that the orbital changes which account for the exophthalmos are responsible also for the lesions of the optic nerve. It is necessary to explain both the loss of vision and the edema of the disk, which can occur separately or in combination. Fuchs[26] stated that exophthalmos is caused most frequently by an increase in the volume of the orbital tissue. As long as the protrusion of the eye is but slight, the optic nerve

> "is subject to no undue tension, its normal S-shaped curve . . . being simply straightened out; it is not until the eye is caused to protrude pretty far that the optic nerve is put on the stretch. If this stretching takes place gradually, the nerve fibers often accommodate themselves to it in a wonderful fashion, so that they preserve their conductivity, and vision is maintained intact; but if the

exophthalmos increases rapidly, the optic nerve owing to the traction soon loses its conducting power."

Hermann[33] thought that the central scotoma in her case was due to severe stretching of the retrobulbar portion of the optic nerve. The scotoma was no longer present 15 months after decompression of the orbit and Roentgen irradiation of the pituitary. Hedges and Scheie[32] favored the explanation that increase in tissue volume and subsequent rise in orbital pressure lead to pressure on the optic nerve and impairment of its circulation, which affect the maculopapillar bundle predominantly. They suggested that the lack of evidence of venous congestion in many cases is due to the fact that the orbital pressure exerts its effect first in the posterior part of the orbit and that vascular stasis becomes manifest by intra-ocular changes only when there is profound increase in the tissue volume of the orbit. Igersheimer[34] thought that the failure of vision in his cases, in which there was no visible edema of the disks, was probably the result of pressure on the optic nerve near, or in front of, the optic foramen, where mainly the papillomacular bundle and its surroundings are involved. Poppen[53] stated:

"Marked pallor of the head of the optic nerve is occasionally seen with associated reduction in vision. This is probably due to the increase in the bulk of tissue in a very confined region (the annulus of Zinn) in which very little fatty tissue is present, thus permitting very little self decompression by absorption of fat. The increased pressure in this constricted area causes direct pressure on the optic nerve and interferes with the blood supply to the nervous tissue itself."

Igersheimer[34] thought that the fact that papilledema in malignant exophthalmos is accompanied by failure of vision demonstrates that it differs in pathogenesis from the papilledema caused by increased intracranial pressure. The high tension from which the orbital contents suffer is comparable in effect, he thought, to that of a tumor in the orbit. Woods[68] stated that pressure changes may occur in the optic nerve when there is marked orbital edema in cases of progressive exophthalmic ophthalmoplegia. These changes begin usually as blurring of the disk margins. Later, actual elevation of the nerve head is produced by venous stasis caused by the orbital hyperplasia. Prolonged pressure may lead to actual death of the nerve fibers from secondary optic atrophy in the late stages of the exophthalmos.

Hermann[33] stated:

"Proptosis is directly caused by oedema of the orbital contents; it is part of the oedematous complex of the syndrome. Swelling of the lids and infraorbital tissues and especially chemosis and papilloedema are also initially the direct result of the orbital oedema; as intraorbital pressure rises, venous drainage becomes difficult and congestion is superimposed on the oedema and can often be seen at the conjunctival and retinal veins."

However, Mulvany[49] expressed the opinion that edema of the lids and conjunctiva is due to obstruction of the palpebral veins and not to waterlogging of the retrobulbar tissues. He added:

"Congestion and swelling of the optic disk, often with retinal hemorrhages, is also found and is due to direct pressure of the swollen muscles on the optic vein. Its association is variable and it may be absent in certain severe instances. . . . Provided pressure is relieved before vision has completely failed, a good recovery may be expected, although in severe and long-standing cases some degree of optic atrophy may follow. Complete blindness due to this cause is rare. The interval between papilledema and optic atrophy is usually a few months."

TREATMENT OF THE OPTIC NERVE LESIONS. It is not possible here to review in detail all of the types of treatment which have been proposed for progressive exophthalmos. Some of the measures which are designed to control the

exophthalmos and protect vision will be discussed. The possibility of preventing the conversion of benign into progressive exophthalmos has been considered. Sexton[58] noted that exophthalmos of benign type causes no great concern even in long-standing severe thyrotoxicosis. Progressive or malignant exophthalmos occurs more often following sudden transition from a profound hyperthyroid state to one of euthyroidism or hypothyroidism. While the change is more sudden following thyroidectomy, it has been observed following the use of antithyroid drugs and radioactive iodine (I^{131}) in the treatment of hyperthyroidism. Williams[67] thought that palpebral swelling and infra-orbital fat deposits may be clues to the subsequent development of progressive exophthalmos. When these findings occur in a patient with hyperthyroidism, a plan of treatment directed toward the slow reduction of the hyperthyroidism is advisable. This is best accomplished by graded doses of I^{131} but is not always successful in preventing the progression of exophthalmos. The addition of substitution thyroid therapy in an effort to reduce the amount of thyroid-stimulating hormone is theoretical, and its effectiveness is questionable.

Falconer and Alexander[21] suggested that malignant exophthalmos is a self-limited process and is only indirectly related to the thyroid hormone and to the pituitary thyrotropic hormone. They thought that the administration of thyroid substance would neither prevent nor stay the progress of the exophthalmos. Reeh and Singer[54] stated that medical therapy in cases of thyrotropic exophthalmos is difficult to evaluate because many patients make a spontaneous recovery and many others are treated only when the exophthalmos has reached an irreversible state (fibrosis). Duke-Elder[19] stated that the exophthalmos of exophthalmic ophthalmoplegia is a self-limiting entity and will recede gradually over the course of 6 to 12 months with or without treatment.

Brain[6] said that treatment of endocrine exophthalmos may be directed 1) toward diminution of pituitary secretion, *a*) by the administration of thyroid extract, which is disappointing, *b*) by the administration of sex hormones, which is disappointing, and *c*) by Roentgen irradiation of the pituitary, which is disappointing in general though satisfactory at times; and 2) toward reduction of the volume of the orbital contents by Roentgen irradiation of the orbits or by surgical decompression when severe exophthalmos cannot be controlled otherwise, when the cornea is threatened or when papilledema or primary optic atrophy is present. This usually saves the situation. Brain[6] noted that reports concerning the use of corticotropin and cortisone had been conflicting.

Millikan and Haines[47] stated:

> "Treatment of exophthalmic ophthalmoplegia with iodine, thyroid, corticotropin, cortisone, and roentgen radiation to the pituitary or orbits or both, or combination of these agents has not been followed by consistently favorable response, though in isolated instances regression of symptoms has been noted after each of these procedures. The associated chemosis, swelling of the lids, edema of the conjunctiva and photophobia apparently are more often benefited than the basic exophthalmos and ophthalmoplegia. This failure of a consistent response to varied methods of treatment implies the presence of some degree of irreversibility in the pathologic process, the presence of multiple mechanisms in the pathogenesis, or the existence of a totally unsuspected cause."

In a recent review article, DeVoe[15] stated that there had been no new developments in the treatment of progressive exophthalmos and that it is recognized that results are poor as far as complete cure with regression of the

exophthalmos is concerned, though usually the condition can be arrested without permanent loss of vision. He commented that the question of the value of corticotropin and cortisone in the treatment continued to produce a division of opinions. Kinsell and his co-workers[39] stated that adequate doses of corticotropin and cortisone combined caused significant decrease in the exophthalmos within 48 hours and, if continued, would restore the eyes to normal except for residuals due to previously developed fibrosis. The authors thought that the beneficial effects resulted from a direct lytic action on retrobulbar accumulations of mononuclear cells and fat and from indirect suppression of thyrotropin secretion. By contrast, a panel appointed by the Medical Research Council[7] to investigate the effect of cortisone on exophthalmos found that the exophthalmos was not reduced in 20 of 28 patients with exophthalmic ophthalmoplegia, though the chemosis was improved in 15 patients. None of 10 patients with exophthalmos without ocular muscle weakness was benefited by cortisone therapy. Fifteen patients were hyperthyroid before treatment; the level of thyroid function was depressed in 8 of the 15 by the treatment. It is of interest to note in this connection that Aterman and Greenberg[2] found that 57 of 68 rats treated with cortisone developed protrusion of the eyeballs at some stage of the experiment. Moreover, Smelser and Ozanics[60] demonstrated the effectiveness of ACTH-B and of cortisone in potentiating exophthalmogenic extracts in experimental animals.

Hermann[33] reported good results in all and full recovery in 7 of 12 cases of pituitary exophthalmos treated by Roentgen irradiation of the pituitary. However, four of the patients required additional orbital decompression, two bilateral and two unilateral. Beierwaltes[5] reported that 13 of 28 patients showed a significant response in exophthalmometer measurements to Roentgen irradiation of the pituitary. He stated that malignant exophthalmos usually responds to irradiation if it has been present for less than a year but rarely responds if it has been present for more than 2 years. However, he stated also that a change in the exophthalmos is not to be expected in the first month after the completion of Roentgen therapy; that beginning recession is noted about 3 months after irradiation and that maximal improvement occurs in an average of 19 months. (This delay in response would seem to raise the question of spontaneous recovery.)

Gedda and Lindgren[27] treated 19 patients who had the hyperophthalmopathic type of Graves's disease by Roentgen irradiation of the pituitary and orbits. Ten were treated by irradiation of the pituitary and posterior parts of the orbits, with definite benefit in all cases. In 6 cases additional irradiation was given to the anterior part of the orbits; satisfactory results were obtained in four. Only the orbits were irradiated in 3 cases; good results were obtained in two. Roentgen treatment of the pituitary region depressed thyroid function in all of the 10 patients who were originally hyperthyroid. Fossati, Silvestrini and Melloni[22] followed the blood thyrotropin levels before, during and after Roentgen irradiation of the pituitary; the serum thyrotropin level was constantly decreased after the treatment.

There seems to be quite general agreement that involvement of the optic nerve is an indication for orbital decompression. Thus Walsh[65] said that pronounced edema of the lids with papilledema or neuroretinal edema, corneal clouding or corneal ulceration in the presence of increased intra-

orbital pressure are indications for decompression of the orbit. Hermann[33] stated that orbital decompression is reserved for cases in which there is rapidly increasing congestion with edema of the optic disk or cases in which there is a visual defect from stretching of the optic nerve or from retinal detachment. Moreover, Cordes[10] said, "If the exophthalmos has progressed until there is danger of corneal ulceration or if there is loss of field or of vision due to edema or to stretching of the optic nerve, surgery is indicated." Naffziger[50] stated that cases of orbital decompression are selected on the basis of continued progression and loss of visual acuity. Diplopia and limitation of ocular movements are not in themselves indications for decompression. Following operation, after stabilization in the position of the globe occurs, the decrease from the preoperative exophthalmometer measurements averages 4 to 5 mm. More striking is the decrease in retrobulbar pressure, as manifest on palpation and backward pressure on the globe. This allows the choked disks to subside and vision to be restored in cases in which the loss of vision has been caused by increased retrobulbar tension with circulatory disturbance in the optic nerve. In Naffziger's[50] opinion it is essential to remove a large section of the orbital roof but it is not necessary to remove the roof of the optic canal. However, Givner and his associates[28] reported a case in which vision returned to normal on the side on which the optic canal was unroofed but failed further, with the development of optic atrophy, on the side on which the canal was not unroofed. This experience led them to advise complete uncapping of the optic foramen in cases in which vision is impaired by involvement of the optic nerve.

Welti[66] reported the results of decompression of the orbit in 10 cases of malignant exophthalmos. Good results were obtained in 6 of the 9 cases in which there was loss of vision. Improvement took place in all of the 4 patients who had normal fundi at the time of the decompression, and in 2 of the 4 with papilledema. Pallor of the disk was noted following the decompression in one eye with papilledema in which the vision did not improve. Pallor of the disks was present before operation in the other case in which vision was not improved by orbital decompression. The orbit was decompressed in two of Igersheimer's[34] cases, with resultant rapid improvement and recovery of practically normal vision. The fundi were normal in both of these cases.

Poppen[53] reported the results of bilateral orbital decompression in 78 patients with thyroid disease. Definitely diminished vision, varying from mild reduction in visual acuity to almost complete blindness, was noted in 51% of the patients before decompression. In 12% of the cases, vision diminished temporarily after the operation; within a few weeks, however, vision improved markedly over that present before the decompression. Vision improved very little if any in 10% of the cases. A patient who had 20/100 vision, a complete quadrantic field defect and pallor of the disk before operation became blind after the decompression.

It would seem then that decompression of the orbit, although it is only a palliative procedure, is the best means available at present for the protection of the cornea and optic nerve until the disease has run its natural course. To obtain the best results, operation should not be delayed until pallor of the disk develops but should be done as soon as possible after the appearance of evidence of optic nerve involvement. As noted by Cordes[10], the lateral wall of the orbit should be removed as well as the orbital roof.

ADDENDUM. Since this review was completed, my attention has been called to an article by I. C. Gilliland and J. I. Strudwick (Brit. Med. J., **1**, 378, 1956) in which further evidence is presented that the exophthalmos-producing factor is distinct from the thyroid-stimulating hormone.

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BOOK REVIEWS AND NOTICES

MEDICAL RESEARCH: A MIDCENTURY SURVEY. VOL. 1. AMERICAN MEDICAL RESEARCH: IN PRINCIPLE AND PRACTICE. VOL. 2: UNSOLVED CLINICAL PROBLEMS: IN BIOLOGICAL PERSPECTIVE. Pp. 765 and 740 respectively. New York: American Foundation, 1955. Price, $15.00 for two volumes.

THE American Foundation set itself the task of evaluating American medical research at this time and has reported its findings in these two volumes. The presentation begins with an assessment of medical research in the perspective of the biological, chemical, physical and mathematical sciences. Then follows a discussion of current trends and current problems in medical and biological research. The next section deals with the research agencies, and the closing section of the first volume discusses the publication and the control of the products of medical research.

The second volume is devoted to a more detailed survey of research activities throughout the land and over several decades as exemplified in nine major unsolved clinical problems. These include cancer, infertility, arteriosclerosis, hypertension, rheumatic syndromes, tuberculosis, the nature of viruses and of virus diseases, alcoholism and schizophrenia. The work is, of course, of primary interest to those who are themselves concerned with any basic and clinical research in the medical sciences. But the work also is filled with instructive material for all clinicians and, by reason of unusual clarity of presentation, for layman concerned with the organization and support of such research programs wherever they be. The work is truly brilliant in its conception and magnificent in its execution.

R. K.

CLINICAL DISORDERS OF HYDRATION AND ACID-BASE EQUILIBRIUM. BY LOUIS G. WELT, M.D., Professor of Medicine, University of North Carolina. Pp. 262; 11 ills. Boston: Little, Brown & Company, 1955. Price, $6.00.

THERE can be no doubt that many lives that would have been lost in years gone by are saved today thanks to the application of modern knowledge of body fluids and electrolytes. The subject is one which is far too extensive for adequate coverage in the usual textbook of medicine, hence the very real need for a book devoted to the subject. The present treatise is written by one who has had extensive experience in this field, and who, happily, has the ability to present a complex subject in a clear, concise, even interesting fashion. Part I deals with Physiologic Considerations and includes the following chapters: Definitions, Volumes and Composion of Body Fluids, Internal Exchanges of Water and Electrolytes, Extrarenal External Exchanges of Electrolytes and Water, Acid-Base Relationships, Renal Physiology, and Consequences of Expansion and Contraction of the Body Fluids. The second part is concerned with Clinical Considerations and is a highly practical discussion of the important disturbances of fluid and acid-base balance, including a splendid presentation of the subject of acute renal insufficiency. The didactic material is well supported by case summaries illustrating the step-by-step management of common problems. A bibliography containing 437 references is appended. With the exception of experts in this field, there are few physicians, be they general practitioners, internists or surgeons who would not profit greatly by a careful study of this book.

T. D.

TUBERCULOSIS. BY CEDRIC SHAW, M.B. Pp. 160; 24 ills. Chicago: Henry Regnery Company, 1955. Price, $2.25.

THIS is one of the Modern Health Series designed, according to Lord Horder the general editor, "to give precise, authoritative information, . . . to tell the truth about diseases as it has never been told to the general public in print before." A generally sound book, it hardly lives up to the editorial promise. Certainly, for the American public, it is inferior to the book by Saul Solomon, M.D. published in 1952.

Certain of the author's statements are open to serious question: "It is this capacity of man to build up his resistance which makes one doubt the wisdom of measures designed to eradicate tuberculosis completely, such as the pasteurization of milk and the destruction of all but attested herds throughout this country." . . . "Liquefaction of the caseous material, which in the process becomes secondarily infected by organisms other than the tubercle bacillus." . . . "It [Isoniazid] has proved to have

a therapeutic effect greater than that of P.A.S. though *less* than that of Streptomycin."

Incidentally, in discussing streptomycin the name Waksman is never mentioned. The casual reader would be justified to believe that the drug had been discovered by Feldman.

The typography is poor, the roentgenographic illustrations are neither well selected nor clearly reproduced. R. C.

BIOCHEMISTRY OF THE DEVELOPING NERVOUS SYSTEM. Proceedings of the First International Neurochemical Symposium, Held at Magdalen College, Oxford, July 13–17, 1954. Edited by HEINRICH WAELSCH, Columbia University and Psychiatric Institute, New York. Pp. 537; illustrated. New York: Academic Press, Inc., 1955. Price, $11.50.

THIS Symposium is the first of a series, the aim of which will be to define and summarize the state of neurochemistry in its varying aspects and implications. An attempt is made to reintegrate biochemical processes with structure and function, particularly with respect to the chemical topography of the brain, which seems of greatest moment in an understanding of function. The program thus includes discussions of morphological and functional ontogeny of the central nervous system, the chemical composition of the developing brain, the blood-brain barrier and gas exchange, intermediary metabolism, enzymatic differentiation in relation to function, cellular chemistry, genetic and hormonal factors, metabolic disturbances, particularly in relation to enzymatic inhibitors. The reader will find a close study of this book extremely rewarding in that the participants of this symposium not only have collected an impressive amount of data but also have frankly discussed areas where intensive work is needed. E. S.

WANTED—TALL MEN. HISTORY OF MEDICINE IN SPRINGFIELD. BY WILLIAM A. R. CHAPIN. Pp. 314; 22 ills. Springfield, Mass.: William A. R. Chapin, M.D., 1955. Price, $4.20.

GOOD local histories of medicine are generally accepted as of value both to the historian as making source material available and as bringing to those already interested in the locality a better knowledge of its worthy past. We should be glad, therefore, for the publication of this carefully prepared and well documented medical history of Springfield, covering from the town's foundation by William Pynchon in 1636 up to the present.

Care of the sick in colonial Springfield appears to have followed the usual primitive course during its first century: being done by nonmedical clericals, lawyers, proprietors and such like. Even through much of the 18th century most "doctors," a term still widely used for all medical men in this country, were self-trained or being apprenticed to an older practitioner. There were few actual M.D.'s in the country before the Revolution, though the term was loosely applied, as indeed in the present work, to a much larger number.

After a nostalgic chapter of personal reminiscences, and brief looks at colonial customs and 17th century medicine in general, Dr. Chapin considers some early Springfield practitioners: John Leonard (who died in 1744; his gravestone is reproduced in the frontispiece), several Coopers, William Pynchon, several descendants of Nathan Smith, and others found in the list of Doctors kept in the Archives of the City Library. In Springfield's oldest Directory (1854) more than a score of physicians are included with such designations as Allopathic, Homeopathic, Clairvoyant, Indian, Botanic, and Eclectic. William Tully (b. 1785) is credited as being Springfield's best known medical man, and J. G. Holland (b. 1819) its best known citizen but more for his literary than his medical achievements.

The hospitals, institutions and health agencies of Springfield and its vicinity, are mentioned in a documented yet readable combination; accompanied by frequent sidelights on the general progress of medicine and local anecdotes. The book is well prepared with easily readable type printed on good paper. Equalized spaces between words help towards pleasant reading, more than compensating for the slight irregularities in the length of the lines. In fact, this setup in itself lends an original touch; we recommend it to bookmakers for further trial. E. K.

NEW EDITIONS

Praktische Mikroskopie. BY EWALD SCHILD. 3rd ed. Pp. 238; 122 ills. Vienna: Wilhelm Maudrich, 1955 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $6.00.

THIS manual furnishes an excellent introduction to practical microscopy. It covers the optics and use of the various microscopes, the prepara-

tion of histological sections, microscopy of urine, blood and sputum, microphotography, and other procedures. It is recommended as a guide for pathologists and laboratory technicians who read German. W. E.

Lehrbuch der Verdauungskrankheiten. By Prof. Dr. Med. Norbert Henning and Doz. Dr. Med. Walther Braumann. 2nd ed. Pp. 562; 335 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $18.35.

This is an excellent textbook for students and practitioners. It should find a wide appeal among those who read German. This, the second edition, has been brought thoroughly up-to-date and is documented by more references to the literature than is usual in a textbook. The illustrations numbering 335, many of them in color, are of outstanding quality, whether they be reproductions of roentgenograms or histologic sections or color photographs. The basic philosophy of the work is in definitely closer agreement with thinking on this side of the Atlantic than has been the case in this field in the past. R. K.

NEW BOOKS

The Mind in Chains. By William L. Moore. Pp. 315. New York: Exposition Press, 1955. Price, $3.50.

This is an autobiography of a young man, an ex-marine with 4 years service, who was hospitalized and received insulin treatment. He keeps a diary of his progress which makes interesting reading for one who would understand the mentally sick person. As the author says, "I wish so desperately to find the words to express my feelings and my thoughts so that you might understand them . . . that you and I might find a bond of friendship and understanding." This kind of understanding is important in the great task of helping the mentally ill back to sanity. O. E.

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